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WO 02/36570 A1

(54) Title: 4-SUBSTITUTED QUINOLINES AS ANTITUMOR AGENTS

(57) Abstract: The invention concerns compounds of formula (I), wherein each of R¹, R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰ m, n, p, X, Y and Z have any meanings defined in the description, processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use as an anti-proliferative agent in the treatment of solid tumour disease.

4-SUBSTITUTED QUINOLINES AS ANTITUMOR AGENTS

The present invention relates to certain novel quinoline derivatives as well as to their use as pharmaceuticals, in particular as inhibitors of specific kinase enzymes, such as MEK enzymes. Further aspects of the invention include pharmaceutical compositions and methods 5 of treatment of proliferative disease such as cancer using said compounds.

Cancer is a disease in which cells grow and divide in an uncontrolled fashion. This uncontrolled growth arises from abnormalities in signal transduction pathways that are used by normal cells to regulate cell growth and division in response to various signalling molecules. Normal cells do not proliferate unless stimulated to do so by specific signal 10 molecules located outside the cell derived from nearby cells or tissues. Growth factors bind to the cell membrane via specific receptors which have intrinsic enzyme activity. These receptors relay the growth signal to the cell nucleus via a series of signalling proteins. In cancer, a number of defects in signal pathways are apparent. For example, cancer cells may produce their own growth factors which bind to their cognate receptors, resulting in an 15 autocrine loop, or receptors may be mutated or overexpressed leading to an increased, continuous signal to proliferate. In addition, negative regulators of cell growth may be lost.

Oncogenes are cancer related genes which often encode abnormal versions of signal pathway components, such as receptor tyrosine kinases, serine-threonine kinases, or downstream signaling molecules such as the ras genes, which code for closely related small 20 guanine nucleotide binding proteins which hydrolyse bound guanosine triphosphate (GTP) to guanosine diphosphate (GDP). Ras proteins are active in promoting cell growth and transformation when they are bound to GTP and inactive when they are bound to GDP. Transforming mutants of p21ras are defective in their GTPase activity and hence remain in the active GTP bound state. The ras oncogene is known to play an integral role in certain cancers, 25 and has been found to contribute to the formation of over 20% of all cases of human cancer.

When activated by ligand, cell surface receptors which are coupled to the mitogenic response, such as growth factor receptors, initiate a chain of reactions which leads to the activation of guanine nucleotide exchange activity on ras. When in its active GTP-bound state, a number of proteins interact directly with ras at the plasma membrane resulting in signal 30 transmission through several distinct pathways. The best characterised effector protein is the product of the raf proto-oncogene. The interaction of raf and ras is a key regulatory step in the

control of cell proliferation. Ras-mediated activation of the raf serine-threonine kinase in turn activates the dual-specificity MEK (MEK1 and MEK2), which is the immediate upstream activator of mitogen activated protein kinase (MAPKs known as extracellular signal regulated protein kinases or ERK1 and ERK2). To date, no substrates of MEK other than MAPK have 5 been identified, though recent reports indicate that MEK may also be activated by other upstream signal proteins such as MEK kinase or MEKK1 and PKC. Activated MAPK translocates and accumulates in the nucleus, where it can phosphorylate and activate transcription factors such as Elk-1 and Sap1a, leading to the enhanced expression of genes such as that for c-fos.

10 The ras-dependent raf-MEK-MAPK cascade is one of the key signalling pathways responsible for transmitting and amplifying mitogenic signals from cell surface to the nucleus resulting in changes in gene expression and cell fate. This ubiquitous pathway appears essential for normal cell proliferation and constitutive activation of this pathway is sufficient to induce cellular transformation. Transforming mutants of p21ras are constitutively active, 15 resulting in raf, MEK and MAPK activity and cell transformation. Inhibition of MEK activity using either antisense raf, a dominant negative MEK mutant or the selective inhibitor PD098059 have been shown to block the growth and morphological transformation of ras-transformed fibroblasts.

10 The mechanism of activation of raf, MEK and MAPK is through phosphorylation on specific serine, threonine or tyrosine residues. Activated raf and other kinases phosphorylate MEK1 on S218 and S222 and MEK2 on S222 and S226. This results in MEK activation and subsequent phosphorylation and activation of ERK1 on T190 and Y192 and ERK2 on T183 and Y185 by the dual specificity MEKs. Whilst MEK can be activated by a number of protein kinases, and active MAPKs phosphorylate and activate a number of substrate proteins 25 including transcription factors and other protein kinases, MEKs appear specific and sole activators of MAPKs and could act as a focal point for cross-cascade regulation. MEK1 and MEK2 isoforms show unusual specificity and also contain a proline-rich insert between catalytic subdomains IX and X which is not present in any of the other known MEK family members. These differences between MEK and other protein kinases, together with the 30 known role of MEK in proliferative signalling suggest that it may be possible to discover and employ selective MEK inhibitors as therapeutic agents for use in proliferative disease.

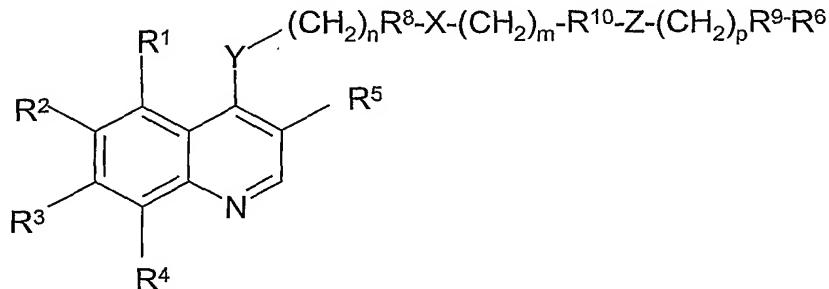
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WO 98/43960 discloses a range of 3-cyano quinoline compounds and their use in the treatment of cancer. Certain of the compounds are demonstrated as being inhibitors of Epidermal Growth Factor Receptor Kinase, and to inhibit cancer cell growth. Other quinoline derivatives which inhibit the effect of growth factors such as VEGF are described in 5 WO98/13350.

Copending but unpublished patent application nos PCT/GB00/01697, PCT/GB00/01707 and PCT/GB00/01698 describe a series of quinoline compounds which are inhibitors of the kinase activity of MEK and as a result, can produce therapeutically useful effects in the treatment of proliferative disease and in particular cancer. The applicants have 10 found that further such compounds and in particular those which have a substituent at the 4-position on the quinolines which includes 3 rings interposed with heteroatoms or chains including heteroatoms, have particularly good activity.

According to a first feature of the present invention there is provided a compound of formula (I)

15



or a pharmaceutically acceptable salt, pro-drug or solvate thereof

20 wherein:

n is 0 or 1;

Y is selected from -NH-, -O-, -S-, or -NR⁷- where R⁷ is alkyl of 1-6 carbon atoms;

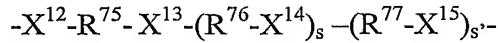
R⁵ is cyano, fluoro, chloro or bromo;

R⁸ is a divalent cycloalkyl of 3 to 7 carbon atoms, which may be optionally further substituted

25 with one or more alkyl of 1 to 6 carbon atom groups; or is a divalent pyridinyl, pyrimidinyl, or phenyl ring, wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally further substituted with one or more groups selected from halogen, alkyl of 1-6 carbon atoms, alkenyl

of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, 5 phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino; X is selected from $-\text{NH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{CH}_2-$ or $-\text{NR}^7-$ where R^7 is alkyl of 1-6 carbon atoms; m and p are independently selected from 0, 1, 2 or 3;

10 R^{10} is an optionally substituted arylene, optionally substituted C_{3-10} cycloalkylene ring or optionally substituted divalent heterocyclic ring or an N-oxide of any nitrogen containing ring, $-\text{Z}-$ is a direct bond or a group of sub-formula (i)



(i)

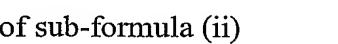
15 where X^{12} , X^{13} each X^{14} and each X^{15} are independently selected from $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{NR}^{78}\text{C}(\text{O})-$, $-\text{NR}^{78}\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NR}^{79}-$, $-\text{C}(\text{O})\text{ONR}^{79}-$, $-\text{SO}_2\text{NR}^{80}-$, $-\text{NR}^{81}\text{SO}_2-$ or $-\text{NR}^{82}-$ (wherein R^{78} , R^{79} , R^{80} , R^{81} and R^{82} each independently represents hydrogen, C_{1-3} alkyl optionally substituted by hydroxy, or C_{1-3} alkoxy C_{2-3} alkyl) and each X^{13} , X^{14} and X^{15} may additionally be a direct bond;

20 s and s' are independently selected from 0, 1, 2 or 3 ;

R^{75} , R^{76} and R^{77} are independently selected from C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene optionally substituted by halo and hydroxy or R^{75} , R^{76} and R^{77} can each independently be direct bonds;

R^9 is an optionally substituted divalent heterocyclic group, C_{1-5} alkylene, or divalent C_{3-7} cycloalkyl;

25 R^6 is hydrogen, amino or a group of sub-formula (ii)



(ii)

where X^{16} , X^{18} and each X^{17} are each independently selected from a direct bond, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{NR}^{86}\text{C}(\text{O})-$, $-\text{NR}^{86}\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NR}^{87}-$, $-\text{C}(\text{O})\text{ONR}^{87}-$, $-\text{SO}_2\text{NR}^{88}-$,

-NR⁸⁹SO₂- or -NR⁹⁰- (wherein R⁸⁶, R⁸⁷, R⁸⁸, R⁸⁹ and R⁹⁰ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl),

R⁸³ and each R⁸⁴ are independently selected from C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋₆alkynylene;

5 R⁸⁵ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl, t is 0, 1, 2 or 3; R¹, R², R³, R⁴ are independently selected from hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, -NR¹¹R¹²- (wherein R¹¹ and R¹², which may be the same or different each represents hydrogen, or C₁₋₃alkyl), 5-6-membered saturated heterocyclic group 10 with 1-2 heteroatoms, selected independently from O, S and N, or a group R¹³-X¹-(CH₂)_x wherein x is 0 or an integer of from 1 to 3, X¹ represents a direct bond, -O-, -CH₂-, -OC(O)-, -C(O)-, -S-, -SO-, -SO₂-, -NR¹⁴C(O)-, -NR¹⁴C(O)O-, -C(O)NR¹⁵-, -C(O)ONR¹⁵-, -SO₂NR¹⁶-, -NR¹⁷SO₂- or -NR¹⁸- (wherein R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), and R¹³ is hydrogen, optionally substituted 15 hydrocarbyl, or optionally substituted heterocyclyl, provided that:

i) where the group of sub-formula (ii) is C₁₋₆alkyl or R⁶ is hydrogen and R⁹ is a divalent heterocyclyl, Z is other than a direct bond, or the group -Z(CH₂)_p- is other than C₂ alkylene, or the group of sub-formula (i) is other than -S-;

20 ii) the group R⁹-R⁶ cannot together be C₁₋₅ alkyl, C₂₋₆ alkenyl, C₂₋₆alkynyl or (C₁₋₅ alkylene)OH unless

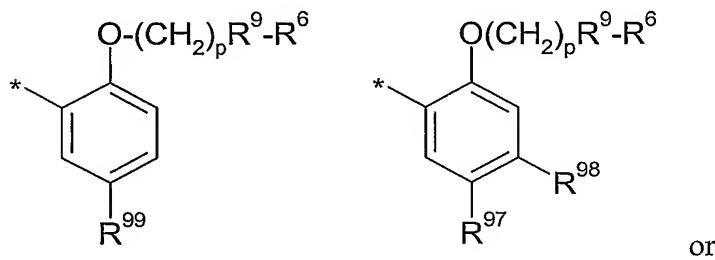
a) in the group of sub-formula (i), R⁷⁵ or R⁷⁶ is the group -C(R^AR^B)- where R^A and R^B are each independently selected from C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl and halo;

25 b) in the group of sub-formula (i), where the terminal group X¹², X¹³ or X¹⁴ linked to -(CH₂)_p- or -R⁹, is selected from -CONR⁷⁹-; -C(O)ONR⁷⁹; -SO₂NR⁸⁰ and -NR⁷⁸C(O); then R⁷⁸, R⁷⁹, and R⁸⁰ are other than hydrogen but when X¹³ is -C(O)NR⁷⁹ then R¹⁰ cannot be pyridyl;

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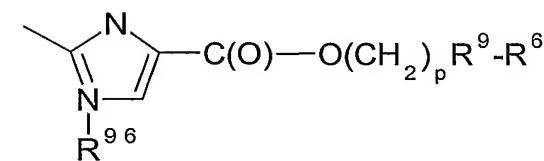
c) the group of sub-formula (i) is selected from $-\text{C}(\text{O})-\text{NR}^{82}-\text{O}-$ and $-\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{NR}^{82}-\text{CH}_2-\text{C}(\text{O})\text{O}-$, where R^{82} is other than hydrogen;

5 d) the group $-\text{R}^{10}-\text{Z}-(\text{CH}_2)_p\text{R}^9-\text{R}^6$ is selected from



or

10

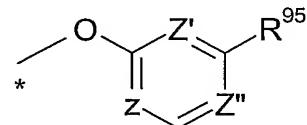


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where R^{99} is selected from $-\text{NC}(\text{O})\text{CH}_3$, $-\text{NC}_2\text{H}_5$ or $-\text{OCH}_3$;
 R^{97} and R^{98} are each independently selected from hydrogen and fluoro, provided that at least one of R^{97} and R^{98} is fluoro;
* denotes the point of attachment; and
15 p , R^9 and R^6 are as hereinbefore defined;

e) the group

$\text{X}-(\text{CH}_2)_m-\text{R}^{10}-\text{Z}-(\text{CH}_2)_p\text{R}^9-\text{R}^6$ is



20

where * denotes the point of attachment to R^8 ;
 R^{95} is selected from $-\text{C}(\text{O})\text{NR}^{94}\text{R}^{93}$ and C_{1-6} alkoxy, where R^{93} and R^{94} each independently represents hydrogen or C_{1-3} alkyl;

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Z, Z', Z'' each independently represent $-\text{CH}-$ or nitrogen and provided that at least one of Z, Z', Z'' is nitrogen;

iii) where the group of sub-formula (i) comprises the group

5 $-\text{X}^{12}-\text{R}^{75}-\text{X}^{13}-(\text{R}^{76}-\text{X}^{14})_s-(\text{R}^{77}-\text{X}^{15})_{s'}-$

where X^{12} is selected from $-\text{O}-$, $-\text{NR}^{82}-$, or $-\text{NR}^{78}\text{C}(\text{O})-$;

X^{13} is selected from $-\text{C}(\text{O})\text{NR}^{79}$, a direct bond or $-\text{NR}^{82}-$;

$\text{R}^{76}, \text{X}^{14}, \text{R}^{77}, \text{X}^{15}, s$ and s' are as hereinbefore defined; then

R^{75} is $\text{C}(\text{R}^{\text{A}}\text{R}^{\text{B}})$ where R^{A} and R^{B} are each independently selected from C_{1-3} alkyl, C_{2-3}

10 alkenyl, C_{2-3} alkynyl and halo; unless

(i) R^9 is piperazinyl linked through the nitrogen atoms or pyridyl;

(ii) R^{75} is 1-3 alkyl substituted by hydroxy; or

(iii) R^{79} is other than hydrogen; or

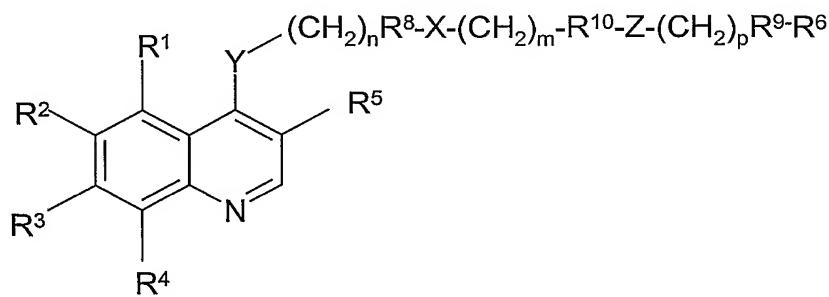
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iv) where the group of sub-formula (i) is selected from $-(\text{CH}_2)_2\text{C}(\text{O})-$ or

$-\text{O}-(\text{CH}_2)_2$ and R^9 is a divalent heterocyclic group, then R^6 is other than hydrogen.

According to another aspect of the first feature of the present invention there is provided a compound of formula (I')

20



(I')

or a pharmaceutically acceptable salt thereof

25 wherein:

n is 0-1;

Y is selected from $-\text{NH}-$, $-\text{O}-$, $-\text{S}-$, or $-\text{NR}^7-$ where R^7 is alkyl of 1-6 carbon atoms;

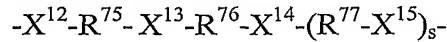
-8-

R^5 is cyano, fluoro, chloro or bromo;

R^8 is a divalent cycloalkyl of 3 to 7 carbon atoms, which may be optionally further substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a divalent pyridinyl, pyrimidinyl, or phenyl ring, wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally further

5 substituted with one or more groups selected from halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, 10 phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino; X is selected from $-NH-$, $-O-$, $-S-$, $-CH_2-$ or $-NR^7-$ where R^7 is alkyl of 1-6 carbon atoms; m and p are independently selected from 0, 1, 2 or 3

15 R^{10} is an optionally substituted arylene, optionally substituted C_{3-10} cycloalkylene ring or optionally substituted divalent heterocyclic ring or an N-oxide of any nitrogen containing ring, $-Z-$ is a direct bond or a group of sub-formula (i)



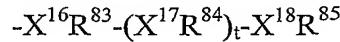
(i)

20 where X^{12} , X^{13} , X^{14} and each X^{15} are independently selected from $-O-$, $-C(O)-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{78}C(O)-$, $-NR^{78}C(O)O-$, $-CONR^{79}-$, $-C(O)ONR^{79}-$, $-SO_2NR^{80}-$, $-NR^{81}SO_2-$ or $-NR^{82}-$ (wherein R^{78} , R^{79} , R^{80} , R^{81} and R^{82} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and X^{15} may additionally be a bond; s is 0, 1, 2 or 3;

25 R^{75} , R^{76} and R^{77} are independently selected from C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene

and R^9 is an optionally substituted divalent heterocyclic group,

R^6 is a group of sub-formula (ii)



(ii)

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where X^{16} , X^{18} and each X^{17} are each independently selected from a direct bond, -O-, -C(O)-, -S-, -SO-, -SO₂-, -NR⁸⁶C(O)-, -NR⁸⁶C(O)O-, -CONR⁸⁷-, -C(O)ONR⁸⁷-, -SO₂NR⁸⁸-, -NR⁸⁹SO₂- or -NR⁹⁰- (wherein R⁸⁶, R⁸⁷, R⁸⁸, R⁸⁹ and R⁹⁰ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl),

5 R⁸³ and each R⁸⁴ are independently selected from C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋₆alkynylene,

R⁸⁵ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl,

t is 0, 1, 2 or 3,

provided that where the group of sub-formula (ii) is C₁₋₆alkyl, Z is other than a direct bond,

10 and

R¹, R², R³, R⁴ are independently selected from hydrogen, hydroxy, halogeno, cyano, nitro,

C₁₋₃alkyl, -NR¹¹R¹²- (wherein R¹¹ and R¹², which may be the same or different each represents hydrogen, or C₁₋₃alkyl), or a group R¹³-X¹-(CH₂)_x wherein x is 0 or an integer of from 1 to 3,

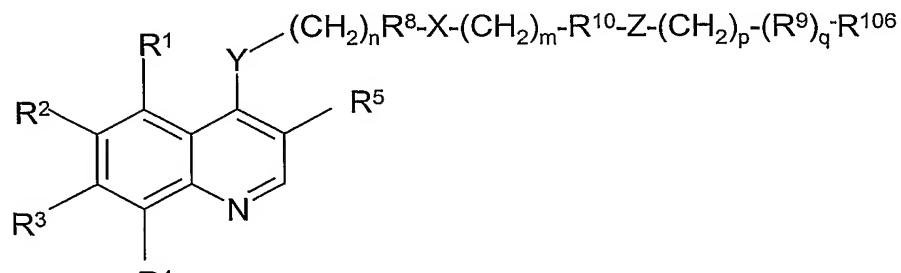
X¹ represents a direct bond, -O-, -CH₂-, -OC(O)-, -C(O)-, -S-, -SO-, -SO₂-, -NR¹⁴C(O)-,

15 -NR¹⁴C(O)O-, -C(O)NR¹⁵-, -C(O)ONR¹⁵-, -SO₂NR¹⁶-, -NR¹⁷SO₂- or -NR¹⁸- (wherein R¹⁴,

R¹⁵, R¹⁶, R¹⁷ and R¹⁸ each independently represents hydrogen, C₁₋₃alkyl or

C₁₋₃alkoxyC₂₋₃alkyl)), and R¹³ is hydrogen, optionally substituted hydrocarbyl, or optionally substituted heterocyclyl.

According to a second feature of the present invention there is provided a compound
20 of formula (IA)



25 or a pharmaceutically acceptable salt, pro-drug or solvate thereof

wherein:

n is 0 or 1;

-10-

Y is selected from $-\text{NH-}$, $-\text{O-}$, $-\text{S-}$, or $-\text{NR}^7-$ where R^7 is alkyl of 1-6 carbon atoms;

R^5 is cyano, fluoro, chloro or bromo;

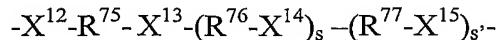
R^8 is a divalent cycloalkyl of 3 to 7 carbon atoms, which may be optionally further substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a divalent pyridinyl, pyrimidinyl,

5 or phenyl ring, wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally further substituted with one or more groups selected from halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, 10 nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino;

X is selected from $-\text{NH-}$, $-\text{O-}$, $-\text{S-}$, $-\text{CH}_2-$ or $-\text{NR}^7-$ where R^7 is alkyl of 1-6 carbon atoms;

15 m, p and q are independently selected from 0, 1, 2 or 3

R^{10} is an optionally substituted arylene, optionally substituted C_{3-10} cycloalkylene ring or optionally substituted divalent heterocyclic ring or an N-oxide of any nitrogen containing ring, -Z- is a group of sub-formula (i)



20

(i)

where X^{12} , X^{13} , each X^{14} and each X^{15} are independently selected from $-\text{O-}$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O-}$, $-\text{S-}$, $-\text{SO-}$, $-\text{SO}_2-$, $-\text{NR}^{78}\text{C}(\text{O})-$, $-\text{NR}^{78}\text{C}(\text{O})\text{O-}$, $-\text{CONR}^{79}-$, $-\text{C}(\text{O})\text{ONR}^{79}-$, $-\text{SO}_2\text{NR}^{80}-$, $-\text{NR}^{81}\text{SO}_2-$ or $-\text{NR}^{82}-$ (wherein R^{78} , R^{79} , R^{80} , R^{81} and R^{82} each independently represents hydrogen, C_{1-3} alkyl optionally substituted by hydroxy, or C_{1-3} alkoxy C_{2-3} alkyl) and each X^{13} ,

25 X^{14} and X^{15} may additionally be a direct bond;

s and s' are independently selected from 0, 1, 2 or 3;

R^{75} is group $-\text{C}(\text{R}^{\text{A}}\text{R}^{\text{B}})-$ where R^{A} and R^{B} are each independently selected from C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and halo;

R^{76} and R^{77} are independently selected from C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene
30 optionally substituted by halo and hydroxy or R^{76} or R^{77} can each independently be a direct bond;

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R^9 is an optionally substituted divalent heterocyclic group, C_{1-5} alkylene, or divalent C_{3-7} cycloalkyl;

R^{106} is hydrogen, hydroxy, amino or a group of sub-formula (ii)

$-X^{16}R^{83}-(X^{17}R^{84})_t-X^{18}R^{85}$

5

(ii)

where X^{16} , X^{18} and each X^{17} are each independently selected from a direct bond, -O-, -C(O)-, -S-, -SO-, -SO₂-, -NR⁸⁶C(O)-, -NR⁸⁶C(O)O-, -C(O)NR⁸⁷-, -C(O)ONR⁸⁷-, -SO₂NR⁸⁸-, -NR⁸⁹SO₂- or -NR⁹⁰- (wherein R^{86} , R^{87} , R^{88} , R^{89} and R^{90} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl);

10 R^{83} and each R^{84} are independently selected from C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene;

R^{85} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl,

t is 0, 1, 2 or 3; and

R^1 , R^2 , R^3 , R^4 are independently selected from hydrogen, hydroxy, halogeno, cyano, nitro,

15 trifluoromethyl, C_{1-3} alkyl, -NR¹¹R¹²- (wherein R^{11} and R^{12} , which may be the same or different each represents hydrogen, or C_{1-3} alkyl), 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, or a group $R^{13}-X^1-(CH_2)_x$

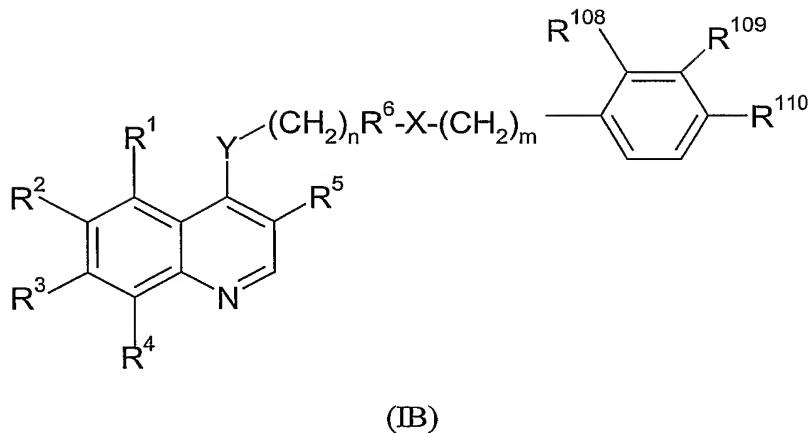
wherein x is 0 or an integer of from 1 to 3, X^1 represents a direct bond, -O-, -CH₂-, -OC(O)-, -C(O)-, -S-, -SO-, -SO₂-, -NR¹⁴C(O)-, -NR¹⁴C(O)O-, -C(O)NR¹⁵-, -C(O)ONR¹⁵-, -SO₂NR¹⁶-,

20 -NR¹⁷SO₂- or -NR¹⁸- (wherein R^{14} , R^{15} , R^{16} , R^{17} and R^{18} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl), and R^{13} is hydrogen, optionally substituted hydrocarbyl, or optionally substituted heterocyclyl.

According to a third feature of the present invention there is provided a compound of formula (IB)

25

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or a pharmaceutically acceptable salt, prodrug or solvate thereof

5 wherein:

n is 0 or 1;

Y is selected from -NH-, -O-, -S-, or -NR⁷ where R⁷ is alkyl of 1-6 carbon atoms;

R⁵ is cyano, fluoro, chloro or bromo;

R⁶ is a divalent cycloalkyl of 3 to 7 carbon atoms, which may be optionally further substituted

10 with one or more alkyl of 1 to 6 carbon atom groups; or is a divalent pyridinyl, pyrimidinyl, or phenyl ring, wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally further substituted with one or more groups selected from halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxyethyl of 2-7 carbon atoms, alkanoyloxyethyl of 2-7 carbon atoms,

15 alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino;

20 X is selected from -NH-, -O-, -S-, -CH₂ or -NR¹⁰⁷ where R¹⁰⁷ is alkyl of 1-6 carbon atoms;

m is 0, 1, 2 or 3

R¹⁰⁸ and R¹⁰⁹ together with the carbon atoms to which they are attached form a fused 5 or 6 membered heteroaryl or heterocyclic ring;

R^{110} is hydrogen or a group $X'R^{110'}$ where X' is NH -, $-O$ -, $-S$ -, $-NR^{107''}$ - where $R^{107''}$ is alkyl of 1-6 carbon atoms and $R^{110'}$ is an optionally substituted alkyl;

R^1, R^2, R^3, R^4 are independently selected from hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, $C_{1-3}alkyl$, $-NR^{11}R^{12-}$ (wherein R^{11} and R^{12} , which may be the same or

5 different each represents hydrogen, or $C_{1-3}alkyl$), 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, or a group $R^{13}-X^1-(CH_2)_x$ wherein x is 0 or an integer of from 1 to 3, X^1 represents a direct bond, $-O$ -, $-CH_2$ -, $-OC(O)-$, $-C(O)-$, $-S$ -, $-SO$ -, $-SO_2$ -, $-NR^{14}C(O)-$, $-NR^{14}C(O)O-$, $-C(O)NR^{15-}$, $-C(O)ONR^{15-}$, $-SO_2NR^{16-}$, $-NR^{17}SO_2-$ or $-NR^{18-}$ (wherein R^{14} , R^{15} , R^{16} , R^{17} and R^{18} each independently represents

10 hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$), and R^{13} is hydrogen, optionally substituted hydrocarbyl, or optionally substituted heterocyclyl;

provided that:

- i) when R^{108} and R^{109} together with the phenyl group form benzofuran, where the heteratom containing ring is substituted with one or more groups independently selected from $C_{1-6}alkyl$, halo, hydroxyl, halo, $-NR^{119}R^{120}$, $C(O)NR^{119}R^{120}$ wherein R^{119} and R^{120} , which may be the same or different, each represent hydrogen or $C_{1-4}alkyl$ or $C_{1-4}cycloalkyl$; or
- ii) when R^{108} and R^{109} together with the phenyl group form benzodihydrofuran or benzoxazole, the heteratom containing ring is substituted with one or more groups independently selected from halo, hydroxyl, halo, $-NR^{119}R^{120}$, $-C(O)NR^{119}R^{120}$ wherein R^{119} and R^{120} , which may be the same or different, each represent hydrogen or $C_{1-4}alkyl$ or $C_{1-4}cycloalkyl$.

In the compounds of formula (IB), R^{108} and R^{109} together with the phenyl to which they are attached preferably from a group selected from benzofuran, indole and quinoline. The indole and quinoline are optionally substituted with one or more groups independently selected from $C_{1-6}alkyl$, halo, hydroxyl, halo, $-NR^{119}R^{120}$, $C(O)NR^{119}R^{120}$ wherein R^{119} and R^{120} which may be the same or different each represent hydrogen or $C_{1-4}alkyl$ or $C_{1-4}cycloalkyl$. Preferably the substituent on the benzofuran or indole is $-C(O)NR^{119}R^{120}$ wherein R^{119} and R^{120} which may be the same or different each represent hydrogen or $C_{1-4}alkyl$ or $C_{1-4}cycloalkyl$. More preferably in the group of formula $-C(O)NR^{119}R^{120}$, R^{119} is hydrogen and R^{120} is selected from $-CH_3$, $-C(CH_3)_2$ and cyclopropyl.

In this specification the term 'alkyl' when used either alone or as a suffix includes straight chained, branched structures. Unless otherwise stated, these groups may contain up to 10, preferably up to 6 and more preferably up to 4 carbon atoms. Similarly the terms "alkenyl" and "alkynyl" refer to unsaturated straight or branched structures containing for example from 5 2 to 10, preferably from 2 to 6 carbon atoms. Cyclic moieties such as cycloalkyl, cycloalkenyl and cycloalkynyl are similar in nature but have at least 3 carbon atoms. Terms such as "alkoxy" comprise alkyl groups as is understood in the art.

The term "halo" or "halogeno" includes fluoro, chloro, bromo and iodo. References to aryl groups include aromatic carbocyclic groups such as phenyl and naphthyl. The term 10 "heterocyclyl" or "heterocyclic" includes aromatic or non-aromatic rings, for example containing from 4 to 20, suitably from 5 to 8 ring atoms, at least one of which, and preferably from 1-4 of which is a heteroatom such as oxygen, sulphur or nitrogen. Examples of such groups include furyl, thienyl, pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, 15 quinolinyl, isoquinolinyl, quinoxalinyl, benzothiazolyl, benzoxazolyl, benzothienyl or benzofuryl. Examples of non-aromatic heterocyclyl groups include morpholino, piperidino, azetidine, tetrahydrofuryl, tetrahydropyridyl. In the case of bicyclic rings, these may comprise an aromatic and non-aromatic portion.

"Heteroaryl" refers to those groups described above which have an aromatic character. 20 The term "aralkyl" refers to aryl substituted alkyl groups such as benzyl.

Other expressions used in the specification include "hydrocarbyl" which refers to any structure comprising carbon and hydrogen atoms. The moiety may be saturated or unsaturated. For example, these may be alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl, or combinations thereof.

25 Examples of such combinations are alkyl, alkenyl or alkynyl substituted with aryl, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl, or an aryl, heterocyclyl, alkoxy, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl substituted with alkyl, alkenyl, alkynyl or alkoxy, but others may be envisaged.

In particular hydrocarbyl groups include alkyl, alkenyl, alkynyl, aryl, aralkyl, 30 cycloalkyl, cycloalkenyl or cycloalkynyl.

The term "interposed" used in relation to heteroatoms in hydrocarbyl chains means that the chains include a heteroatom such as sulphur, oxygen or nitrogen either at an intermediate position along their length or at an end of the chain.

The term "interposed" used in relation to heterocyclic rings in hydrocarbyl chains
5 means that the chains include a heterocyclic ring either at an intermediate position along their length or at an end of the chain.

Suitable pharmaceutically acceptable salts of compounds of formula (I), or (IA) or (IB) include acid addition salts such as methanesulfonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. A preferred
10 pharmaceutically acceptable salt is a hydrochloride salt.

Thus, the alkyl portion of the alkyl, alkoxy, alkanoyloxy, alkoxyethyl, alkanoyloxyethyl, alkylsulphanyl, alkylsulphonyl, alkylsulfonamido, carboalkoxy, carboalkyl, alkanoylamino aminoalkyl, alkylaminoalkyl, N,N-dicycloalkylaminoalkyl, hydroxyalkyl, and alkoxyalkyl substituents include both straight chain as well as branched carbon chains. The
15 cycloalkyl portions of N-cycloalkyl-N-alkylaminoalkyl and N,N-dicycloalkylaminoalkyl substituents include both simple carbocycles as well as carbocycles containing alkyl substituents. The alkenyl portion of the alkenyl, alkenoyloxyethyl, alkenyloxy, alkenylsulfonamido, substituents include both straight chain as well as branched carbon chains and one or more sites of unsaturation. The alkynyl portion of the alkynyl, alkynoyloxyethyl,
20 alkynylsulfonamido, alkynylloxy, substituents include both straight chain as well as branched carbon chains and one or more sites of unsaturation. Carboxy is defined as a $-CO_2H$ radical. Carboalkoxy of 2-7 carbon atoms is defined as a $-CO_2R''$ radical, where R'' is an alkyl radical of 1-6 carbon atoms. Carboalkyl is defined as a $-COR''$ radical, where R'' is an alkyl radical of 1-6 carbon atoms. Alkanoyloxy is defined as a $-OCOR''$ radical, where R'' is an alkyl
25 radical of 1-6 carbon atoms. Alkanoyloxyethyl is defined as $R''CO_2CH_2-$ radical, where R'' is an alkyl radical of 1-6 carbon atoms. Alkoxyethyl is defined as $R''OCH_2-$ radical, where R'' is an alkyl radical of 1-6 carbon atoms. Alkylsulphanyl is defined as $R''SO-$ radical, where R'' is an alkyl radical of 1-6 carbon atoms. Alkylsulphonyl is defined as $R''SO_2-$ radical, where R'' is an alkyl radical of 1-6 carbon atoms. Alkylsulfonamido, alkenylsulfonamido,
30 alkynylsulfonamido are defined as $R''SO_2NH-$ radical, where R'' is an alkyl radical of 1-6 carbon atoms, an alkenyl radical of 2-6 carbon atoms, or an alkynyl radical of 2-6 carbon

atoms, respectively. N-alkylcarbamoyl is defined as R"NHCO- radical, where R" is an alkyl radical of 1-6 carbon atoms. N,N-dialkylcarbamoyl is defined as R" R'NCO- radical, where R" is an alkyl radical of 1-6 carbon atoms, R' is an alkyl radical of 1-6 carbon atoms and R', and R" may be the same or different. When X is substituted, it is preferred that it is mono-, 5 di-, or tri-substituted, with monosubstituted being most preferred. It is preferred that of the substituents, R₁, R₂, R₃ and R₄ at least one is hydrogen and it is most preferred that two or three be hydrogen. An azacycloalkyl-N-alkyl substituent refers to a monocyclic heterocycle that contains a nitrogen atom on which is substituted a straight or branched chain alkyl radical. A morpholino-N-alkyl substituent is a morpholine ring substituted on the nitrogen atom with a 10 straight or branch chain alkyl radical. A pipeazino-N-alkyl substituent is a piperazine ring substituted on one of the nitrogen atoms with a straight or branch chain alkyl radical. A N-alkyl-piperidino-N-alkyl substituent is a piperidine ring substituted on one of the nitrogen atoms with a straight or branched chain alkyl group and on the other nitrogen atom with a straight or branch chain alkyl radical.

15 When any group contains an alkyl portion, the alkyl portion contains preferably 1-6 carbon atoms, more preferably 1-4 carbon atoms, particularly methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl or tert-butyl. When any group contains an alkenyl or alkynyl portion, the alkenyl or alkynyl portion contains preferably 2-6 carbon atoms, more preferably 2-4 carbon atoms.

20 The compounds of this invention may contain an asymmetric carbon; in such cases, the compounds of this invention cover the racemate and the individual R and S enantiomers, and in the case were more than one asymmetric carbon exists, the individual diasteromers, their racemates and individual enantiomers.

Preferably R¹, R², R³ and R⁴ are each independently selected from hydrogen, 25 hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, -NR¹¹R¹² (wherein R¹¹ and R¹², which may be the same or different, each represents hydrogen or C₁₋₃alkyl), a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, or a group R¹³-X¹-(CH₂)_x wherein x is 0 to 3, X¹ represents -O-, -CH₂-, -OCO-, carbonyl, -S-, -SO-, -SO₂-, -NR¹⁴C(O)-, -C(O)NR¹⁵-, -SO₂NR¹⁶-, -NR¹⁷SO₂- or -NR¹⁸- 30 (wherein R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹³ is selected from one of the following sixteen groups:

- 1) $C_{1-5}alkyl$ which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, cyano and amino;
- 2) $C_{1-5}alkylX^2COR^{19}$ (wherein X^2 represents $-O-$ or $-NR^{20}-$ (wherein R^{20} represents hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{19} represents $-NR^{21}R^{22}-$ or $-OR^{23}-$ (wherein R^{21} , R^{22} and R^{23} which may be the same or different each represents hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$));
- 3) $C_{1-5}alkylX^3R^{24}$ (wherein X^3 represents $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-OCO-$, $-CO-O-$, $-NR^{25}CO-$, $-CONR^{26}-$, $-SO_2NR^{27}-$, $-NR^{28}SO_2-$ or $-NR^{29}-$ and $C_{1-5}alkyl$ optionally substituted by hydroxy (wherein R^{25} , R^{26} , R^{27} , R^{28} and R^{29} each independently represents hydrogen, $C_{1-3}alkyl$ optionally substituted by hydroxy or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{24} represents hydrogen, amino optionally substituted by $C_{1-5}alkoxycarbonyl$, $C_{1-5}alkyl$, $C_{3-6}cycloalkyl$, phenyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which $C_{1-5}alkyl$ group may bear one or two substituents selected from oxo, hydroxy, halogeno and $C_{1-4}alkoxy$ and which cyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, $C_{1-4}alkyl$, $C_{1-4}hydroxyalkyl$ and $C_{1-4}alkoxy$);
- 4) $C_{1-5}alkylX^4C_{1-5}alkylX^5R^{30}$ (wherein X^4 and X^5 which may be the same or different are each $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{31}CO-$, $-CONR^{32}-$, $-SO_2NR^{33}-$, $-NR^{34}SO_2-$ or $-NR^{35}-$ (wherein R^{31} , R^{32} , R^{33} , R^{34} and R^{35} each independently represents hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{30} represents hydrogen, $C_{1-4}alkanoyl$ or $C_{1-3}alkyl$ optionally substituted by hydroxy);
- 5) $C_{1-5}alkylR^{36}$ (wherein R^{36} is $C_{3-6}cycloalkyl$ or a 4, 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which $C_{3-6}cycloalkyl$ and heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, $C_{1-4}alkyl$, $C_{1-4}hydroxyalkyl$, $C_{1-4}alkoxy$, $C_{2-5}alkenyl$, $hydroxyC_{2-5}alkenyl$, $C_{2-5}alkynyl$, $C_{1-5}alkanoyl$, $C_{1-5}alkoxycarbonyl$, $C_{1-3}alkanoylC_{1-3}alkyl$, $C_{1-3}alkoxyC_{1-3}alkyl$, $C_{1-5}alkylthio$, $C_{1-5}alkylsulphanyl$, $C_{1-5}alkylsulphonyl$, aryl, $hydroxyC_{1-5}alkoxy$, nitro, amino, amino $C_{1-5}alkyl$, guanidino, $N-C_{1-5}alkylamino$, $N,N-di-C_{1-5}alkylamino$, carboxy, cyano, cyano $C_{1-5}alkyl$, $-CONR^zR^{z'}$ and $-NR^{z''}CO-$ (wherein R^z , $R^{z'}$ and $R^{z''}$ each independently represent hydrogen, $C_{1-5}alkyl$ or $C_{1-3}alkoxyC_{1-3}alkyl$);

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6) $(CH_2)_qX^6R^{37}$ (wherein q is an integer from 0 to 5, X^6 represents a direct bond, -O-, -S-, -SO₂-, -NR³⁸CO-, -CONR³⁹-, CO-O-, -SO₂NR⁴⁰-, -NR⁴¹SO₂- or -NR⁴²- (wherein R³⁸, R³⁹, R⁴⁰, R⁴¹ and R⁴² each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁷ is C₁₋₅alkoxy, a phenyl group, a benzyl group, a pyridone group or a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which phenyl, benzyl, pyridone or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, nitro, amino, N-C₁₋₅alkylamino, N,N-di-C₁₋₅alkylamino, guanidino, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄hydroxyalkoxy, C₁₋₄aminoalkyl, C₁₋₄alkylamino, carboxy, cyano, cyanoC₁₋₅alkyl, C₂₋₅alkenyl, hydroxyC₂₋₅alkenyl, C₂₋₅alkynyl, C₁₋₅alkanoyl, C₁₋₅alkoxycarbonyl, C₁₋₃alkanoylC₁₋₃alkyl, C₁₋₃alkoxyC₁₋₃alkyl, C₁₋₅alkylthio, C₁₋₅alkylsulphanyl, C₁₋₅alkylsulphonyl, aryl, -CONR⁴³R⁴⁴ and -NR⁴⁵COR⁴⁶ (wherein R⁴³, R⁴⁴, R⁴⁵ and R⁴⁶, which may be the same or different, each represents hydrogen, C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl));

15 7) C₂₋₆alkenylR³⁶ (wherein R³⁶ is as defined hereinbefore);

8) C₂₋₆alkynylR³⁶ (wherein R³⁶ is as defined hereinbefore);

9) X⁷R⁴⁷ (wherein X⁷ is -SO₂-, -O- or -CONR⁴⁸R⁴⁹- (wherein R⁴⁸ and R⁴⁹, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R⁴⁷ represents C₁₋₅alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino) with the provisos that when X⁷ is -SO₂-, X¹ is -O-; when X⁷ is -O-, X¹ is carbonyl; or when X⁷ is -CONR⁴⁸R⁴⁹-, X¹ is -O- or NR¹⁸ (wherein R⁴⁸, R⁴⁹ and R¹⁸ are as defined hereinbefore);

10) C₂₋₆alkenylR³⁷ (wherein R³⁷ is as defined hereinbefore);

11) C₂₋₆alkynylR³⁷ (wherein R³⁷ is as defined hereinbefore);

25 12) C₂₋₆alkenylX⁸R³⁷ (wherein X⁸ represents -O-, -S-, -SO₂-, -NR⁵⁰CO-, -CONR⁵¹-, -SO₂NR⁵²-, -NR⁵³SO₂- or -NR⁵⁴- (wherein R⁵⁰, R⁵¹, R⁵², R⁵³ and R⁵⁴ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁷ is as defined hereinbefore);

13) C₂₋₆alkynylX⁹R³⁷ (wherein X⁹ represents -O-, -S-, -SO₂-, -NR⁵⁵CO-, -CONR⁵⁶-, -SO₂NR⁵⁷-, -NR⁵⁸SO₂- or -NR⁵⁹- (wherein R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸ and R⁵⁹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁷ is as defined hereinbefore);

30

14) $C_{1-3}alkylX^{10}C_{1-3}alkylR^{37}$ (wherein X^{10} represents -O-, -S-, -SO-, -SO₂-, -NR⁶⁰CO-, -CONR⁶¹-, -SO₂NR⁶²-, -NR⁶³SO₂- or -NR⁶⁴- (wherein R⁶⁰, R⁶¹, R⁶², R⁶³ and R⁶⁴ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁷ is as defined hereinbefore);

5 15) R³⁶ (wherein R³⁶ is as defined hereinbefore); and

16) $C_{1-3}alkylX^{10}C_{1-3}alkylR^{36}$ (wherein X¹⁰ and R³⁶ are as defined hereinbefore).

In particular R¹, R², R³ and R⁴ are selected from hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, -NR¹¹R¹²- (wherein R¹¹ and R¹² are as defined above), or R¹³X¹-(CH₂)_x- (wherein x is 0 or an integer of from 1-3, X¹ represents a direct bond, -O-,

10 -CH₂-, -OC(O)-, -C(O)-, -S-, -SO-, -SO₂-, -NR¹⁴C(O)-, -NR¹⁴C(O)O-, -C(O)NR¹⁵-, -C(O)ONR¹⁵-, -SO₂NR¹⁶-, -NR¹⁷SO₂- or -NR¹⁸- (wherein R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl)), and R¹³ is any one of the following twenty-two groups

1') C₁₋₅alkyl which may be unsubstituted or which may be substituted with one or more

15 groups selected from hydroxy, oxiranyl, fluoro, chloro, bromo and amino (including C₁₋₃alkyl and trifluoromethyl);

2') -R^aX²C(O)R¹⁹ (wherein X² represents -O- or -NR²⁰- (in which R²⁰ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁹ represents C₁₋₃alkyl, -NR²¹R²² or -OR²³ (wherein R²¹, R²² and R²³ which may be the same or different each represents hydrogen, C₁₋₅alkyl.

20 hydroxyC₁₋₅alkyl or C₁₋₃alkoxyC₂₋₃alkyl));

3') -R^bX³R²⁴ (wherein X³ represents -O-, C(O)-S-, -SO-, -SO₂-, -OC(O)-, -NR²⁵C(O)-, -NR²⁵C(O)O-, -C(O)NR²⁶-, -C(O)ONR²⁶-, -SO₂NR²⁷-, -NR²⁸SO₂- or -NR²⁹- (wherein R²⁵, R²⁶, R²⁷, R²⁸ and R²⁹ each independently represents hydrogen, C₁₋₃alkyl, hydroxy C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl and R²⁴ represents hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, cyclopropyl,

25 cyclobutyl, cyclopentyl, cyclohexyl, phenyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₆alkyl group may bear 1, 2 or 3 substituents selected from oxo, hydroxy, halogeno, cyclopropyl, amino, C₁₋₄alkylamino, C₁₋₄alkanoyldi-C₁₋₄alkylamino, C₁₋₄alkylthio, C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano,

30 C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl,

C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino,

di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group $-(\text{O}-)_f(\text{R}^b)^g\text{D}$ (wherein f is 0 or 1, g is 0 or 1 and D is a C₃₋₆cycloalkyl group or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may 5 bear one or more substituents selected from C₁₋₄alkyl));

4') -R^cX⁴R^c' X⁵R³⁰ (wherein X⁴ and X⁵ which may be the same or different are each -O-, C(O), -S-, -SO-, -SO₂-, -NR³¹C(O)-, -NR³¹C(O)O-, -C(O)NR³²-, -C(O)ONR³²-, -SO₂NR³³-, -NR³⁴SO₂- or -NR³⁵- (wherein R³¹, R³², R³³, R³⁴ and R³⁵ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl and R³⁰ represents hydrogen,

10 C₁₋₃alkyl, hydroxyC₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);

5') R^dR³⁶ (wherein R³⁶ is a 4-6-membered cycloalkyl or saturated heterocyclic ring (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which cycloalkyl or heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, cyanoC₁₋₄alkyl, cyclopropyl,

15 C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, carboxamido, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, C₁₋₄alkanoyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy nitro, amino, C₁₋₄alkoxy, C₁₋₄hydroxyalkoxy, carboxy, trifluoromethyl, -C(O)NR⁶⁵R⁶⁶, -NR⁶⁷C(O)R⁶⁸ (wherein R⁶⁵, R⁶⁶, R⁶⁷ and R⁶⁸, which may be the same or different, each 20 represents hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and a group $-(\text{O}-)_f(\text{R}^b)^g\text{ringD}$ (wherein f is 0 or 1, g is 0 or 1 and ring D is a cyclic group selected from C₃₋₆cycloalkyl, aryl or 5-6-membered saturated or unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from halo and C₁₋₄alkyl);

25 6') R^eX⁶R³⁷ (wherein X⁶ represents a direct bond, -O-, -C(O)-, -S-, -SO-, -SO₂-, -NR³⁸CO-, -NR³⁸C(O)O-, -CONR³⁹-, -C(O)ONR³⁹-, -SO₂NR⁴⁰-, -NR⁴¹SO₂- or -NR⁴²- (wherein R³⁸, R³⁹, R⁴⁰, R⁴¹ and R⁴² each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁷ is a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which 30 pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl,

C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, oxo, cyanoC₁₋₄alkyl, cyclopropyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, C₁₋₄alkanoyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy, carboxy, carboxamido, trifluoromethyl, cyano, -C(O)NR⁴³R⁴⁴, 5 -NR⁴⁵C(O)R⁴⁶ (wherein R⁴³, R⁴⁴, R⁴⁵ and R⁴⁶, which may be the same or different, each represents hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and a group -(O-)_f(R^b)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a cyclic group selected from C₃₋₆cycloalkyl, aryl or 5-6-membered saturated or unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or 10 more substituents selected from halo and C₁₋₄alkyl);

7') -R^fR³⁶ (wherein R³⁶ is as defined in (5') hereinbefore);

8') -R^gR³⁶ (wherein R³⁶ is as defined in (5') hereinbefore);

9') X⁷R⁴⁷ (wherein X⁷ is -SO₂-, -O- or -CONR⁴⁸R⁴⁹- (wherein R⁴⁸ and R⁴⁹, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R⁴⁷ 15 represents C₁₋₅alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino) with the provisos that when X⁷ is -SO₂-, X¹ is -O-, when X⁷ is -O-, X¹ is carbonyl, when X⁷ is -CONR⁴⁸R⁴⁹-, X¹ is -O- or NR¹⁸ (wherein R⁴⁸, R⁴⁹ and R¹⁸ are as defined in (6') hereinbefore);

10') -R^hR³⁷ (wherein R³⁷ is as defined in (6') hereinbefore);

20 11') -RⁱR³⁷ (wherein R³⁷ is as defined in (6') hereinbefore);

12') -R^jX⁸R³⁷ (wherein X⁸ represents -O-, -C(O)-, -S-, -SO-, -SO₂-, -OC(O)-, -NR⁵⁰C(O)-, -NR⁵⁰C(O)O-, -C(O)NR⁵¹-, -C(O)ONR⁵¹-, -SO₂NR⁵²-, -NR⁵³SO₂- or -NR⁵⁴- (wherein R⁵⁰, R⁵¹, R⁵², R⁵³ and R⁵⁴ each independently represents hydrogen, C₁₋₃alkyl, hydroxyC₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁷ is as defined in (6') hereinbefore);

25 13') -R^kX⁹R³⁷ (wherein X⁹ represents -O-, C(O), -S-, -SO-, -SO₂-, -NR⁵⁵C(O)-, -NR⁵⁵C(O)O-, -C(O)NR⁵⁶-, -C(O)ONR⁵⁶-, -SO₂NR⁵⁷-, -NR⁵⁸SO₂- or -NR⁵⁹- (wherein R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸ and R⁴⁹ each independently represents hydrogen, C₁₋₃alkyl, hydroxyC₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁷ is as defined in (6') hereinbefore);

14') -R^mX¹⁰R^mR³⁷ (wherein X¹⁰ represents -O-, -C(O)-, -S-, -SO-, -SO₂-, -NR⁶⁰C(O)-,

-NR⁶⁰C(O)O-, -C(O)NR⁶¹-, -C(O)ONR⁶¹-, -SO₂NR⁶²-, -NR⁶³SO₂- or -NR⁶⁴- (wherein R⁶⁰, R⁶¹, R⁶², R⁶³ and R⁶⁴ each independently represents hydrogen, C₁₋₃alkyl, hydroxyC₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁷ is as defined in (6') hereinbefore);

15') R³⁶ (where R³⁶ is as defined in (5') hereinbefore);

5 16') -RⁿX¹⁰R^{n'}R³⁶ (wherein X¹⁰ is as defined in (14') above and R³⁶ is as defined in (5') hereinbefore);

17') -R^pX¹⁰-R^{p'}R³⁷ (wherein X¹⁰ is as defined in (14') above and R³⁷ are as defined in (6') hereinbefore);

18') C₂₋₅alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;

10 19') C₂₋₅alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;

15 20') -R^tX¹⁰R^{t'}R³⁶ (wherein X¹⁰ is as defined in (14') above and R³⁶ is as defined in (5') hereinbefore);

21') -R^uX¹⁰R^{u'}R³⁶ (wherein X¹⁰ is as defined in (14') above and R³⁶ is as defined in (5') hereinbefore); and

22') -R^vR⁶⁹(R^{v'})_{q'}(X¹⁰)_rR⁷⁰ (wherein X¹⁰ is as defined in (14') above, q' is 0 or 1, r is 0 or 1, and R⁶⁹ is a C₁₋₃alkylene group or a cyclic group selected from cyclopropyl, cyclobutyl, cyclopentylene, cyclohexylene or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkylene group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, i(C₁₋₄alkyl)aminoC₁₋₄alkyl,

25 30 C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group

$-(\text{O})_f(\text{R}^b)_g\text{ringD}$ (wherein f is 0 or 1, g is 0 or 1 and ring D is a cyclic group selected from $\text{C}_{3-6}\text{cycloalkyl}$, aryl or 5-6-membered saturated or unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from halo and $\text{C}_{1-4}\text{alkyl}$); and R^{70} is hydrogen, $\text{C}_{1-3}\text{alkyl}$, or a cyclic 5 group selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which $\text{C}_{1-3}\text{alkyl}$ group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $\text{C}_{1-4}\text{alkoxy}$ and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $\text{C}_{1-4}\text{cyanoalkyl}$, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{hydroxyalkyl}$, $\text{C}_{1-4}\text{alkoxy}$, $\text{C}_{1-4}\text{alkoxyC}_{1-4}\text{alkyl}$, 10 $\text{C}_{1-4}\text{alkylsulphonylC}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkoxycarbonyl}$, $\text{C}_{1-4}\text{aminoalkyl}$, $\text{C}_{1-4}\text{alkylamino}$, $\text{di}(\text{C}_{1-4}\text{alkyl})\text{amino}$, $\text{C}_{1-4}\text{alkylaminoC}_{1-4}\text{alkyl}$, $\text{di}(\text{C}_{1-4}\text{alkyl})\text{aminoC}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkylaminoC}_{1-4}\text{alkoxy}$, $\text{di}(\text{C}_{1-4}\text{alkyl})\text{aminoC}_{1-4}\text{alkoxy}$ and a group $-(\text{O})_f(\text{R}^b)_g\text{ringD}$ (wherein f is 0 or 1, g is 0 or 1 and D is a cyclic group selected from $\text{C}_{3-6}\text{cycloalkyl}$, aryl or 15 5-6-membered saturated or unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from halo and $\text{C}_{1-4}\text{alkyl}$); and wherein R^a , R^b , R^b , R^c , R^c , R^d , R^e , R^i , R^m , $\text{R}^{m'}$, R^n , $\text{R}^{n'}$, $\text{R}^{p'}$, $\text{R}^{t'}$, $\text{R}^{u'}$, R^v and $\text{R}^{v'}$ are independently selected from $\text{C}_{1-8}\text{alkylene}$ groups optionally substituted by one or more substituents selected from hydroxy, halogeno, amino; and R^e may additionally be a bond; and 20 R^f , R^h , R^j , R^p and R^t are independently selected from $\text{C}_{2-8}\text{alkenylene}$ groups optionally substituted by one or more substituents selected from hydroxy, halogeno, amino, and R^t may additionally be a bond; and R^g , R^k , and R^u are independently selected from $\text{C}_{2-8}\text{alkynylene}$ groups optionally substituted by one or more substituents selected from hydroxy, halogeno or amino. 25 In one embodiment, at least one group R^1 , R^2 , R^3 or R^4 is a group $\text{R}^{13}\text{X}^1-(\text{CH}_2)_x-$ (wherein x is 0 or an integer of from 1-3, X^1 represents $-\text{NR}^{14}\text{C}(\text{O})\text{O}-$, or $\text{C}(\text{O})\text{ONR}^{15}-$, (wherein R^{13} , R^{14} and R^{15} are as defined above). A particular example of such a group for R^1 , R^2 , R^3 or R^4 is a group $-\text{NHC}(\text{O})\text{OR}^{13}$ where R^{13} is as defined above, and in particular is a group of formula (6') such as benzyl. 30 In particular, at least one group R^1 , R^2 , R^3 or R^4 is selected from $\text{R}^{13}\text{X}^1-(\text{CH}_2)_x-$ (wherein x is 0 or an integer of from 1-3, X^1 represents a direct bond, $-\text{O}-$, $-\text{CH}_2-$, $-\text{OC}(\text{O})-$,

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-C(O)-, -S-, -SO-, -SO₂-, -NR¹⁴C(O)-, -NR¹⁴C(O)O-, -C(O)NR¹⁵-, -C(O)ONR¹⁵-, -SO₂NR¹⁶-, -NR¹⁷SO₂- or -NR¹⁸- (wherein R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl)), and R¹³ is any one of the following twenty-two groups;

5 1'') C₁₋₅alkyl substituted with one or more groups selected from oxiranyl, chloro or bromo; 2'') -R^{a'}X²C(O)R¹⁹ (wherein X² and R¹⁹ are as defined in (2') above, and R^{a'} is a C₁₋₈alkylene groups substituted by one or more substituents selected from hydroxy, halogeno, amino,

3'') -R^{b'}X³R²⁴ (wherein either R²⁴ is any of the groups defined in (3') above and X³ is -

10 C(O), -NR²⁵C(O)O-, -C(O)ONR²⁶- (wherein R²⁵ and R²⁶ are as defined in (3') above), or X³ is any other groups defined in (3') above and R²⁴ represents C₁₋₃alkyl, C₃₋₆alkyl, C₂₋₆alkenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or phenyl, wherein (a) the C₃₋₆alkyl group may bear 1, 2 or 3 substituents selected from oxo, hydroxy, halogeno, cyclopropyl, amino, C₁₋₄alkylamino, C₁₋₄alkanoyldi-C₁₋₄alkylamino, C₁₋₄alkylthio, C₁₋₄alkoxy; (b) the C₁₋₃alkyl group may be similarly substituted to the C₃₋₆alkyl provided it includes at least one substituent selected from cyclopropyl, amino, C₁₋₄alkylamino, C₁₋₄alkanoyldi-C₁₋₄alkylamino, C₁₋₄alkylthio, C₁₋₄alkoxy; (c) the cyclopropyl or cyclobutyl may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl,

20 C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group -(-O-)_f(R^{b'})_gD (wherein f, g R^{b'} and D are as defined above); (d) the cyclopentyl or cyclohexyl may be similarly substituted provided it includes at least one substituent selected from cyano, C₁₋₄cyanoalkyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl,

25 C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group -(-O-)_f(R^{b'})_gD (wherein f, g R^{b'} and D are as defined above), or X³ and R²⁴ are any of the groups defined in 3' above and R^b is other than C₁₋₅alkylene;

30 4'') -R^{c'}X⁴R^{c'}X⁵R³⁰ (wherein R^c, R^{c'} and R³⁰ are as defined in (4') above and X⁴ and X⁵ are as defined above provided at least one of these is selected from C(O), -NR³¹C(O)O-, or

-C(O)ONR³²- (wherein R³¹ and R³² are as defined in (4') above), or X⁴ and X⁵ are any of the groups defined in (4') above, and either R³⁰ is hydroxyC₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), or at least one of R^c or R^{c'} is other than an unsubstituted C₁₋₅alkylene group;

5 5'')R^dR³⁶ (wherein R^d is as defined above, and R³⁶ is a 4-6-membered cycloalkyl or a saturated heterocyclic ring (linked via carbon or nitrogen including for example from 4 to 7 atoms) with 1-2 heteroatoms, selected independently from O, S and N, which cycloalkyl or heterocyclic group may bear 1 or 2 substituents listed in (5') above, provided that where R³⁶ is a 5 or 6 membered heterocyclic ring, either it carries at least one substituent selected from cyano, cyanoC₁₋₄alkyl, cyclopropyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl,

10 carboxamido, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, C₁₋₄alkanoyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy nitro, amino, C₁₋₄hydroxyalkoxy, carboxy, trifluoromethyl, -C(O)NR⁶⁵R⁶⁶, -NR⁶⁷C(O)R⁶⁸ (wherein R⁶⁵, R⁶⁶, R⁶⁷ and R⁶⁸, are as defined in (5') above and a group -(O-)_f(R^b)_gringD (wherein f, g, R^b and D are as defined above); R³⁶ is any of the

15 groups defined in 5' above and R^d is other than C₁₋₅alkyl;

6'') R^eX⁶R³⁷ (wherein R^e and R³⁷ are any of the groups defined above, provided that X⁶ represents -C(O)-, -NR³⁸C(O)O-, or -C(O)ONR³⁹- (wherein R³⁸ and R³⁹ are as defined above) or, X⁶ is any other group listed in (6') above, provided that either R³⁷ is a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group as (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group which is substituted as described in (6') provided it carries at least one substituent selected from nitro, amino, C₁₋₄hydroxyalkoxy, oxo, cyanoC₁₋₄alkyl, cyclopropyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, C₁₋₄alkanoyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy,

20 di(C₁₋₄alkyl)aminoC₁₋₄alkoxy, carboxamido, trifluoromethyl, or a group -(O-)_f(R^b)_gringD (wherein f, g, R^b and D are as defined above) or R^e is other than a direct bond or a C₁₋₅alkylene group;

25 7'') -R^fR³⁶ (wherein R^f and R³⁶ are as defined in (7') above provided that where R^f is unsubstituted C₂₋₆ alkenylene, R³⁶ is as defined in (5'') hereinbefore);

30 8'') -R^gR³⁶ (wherein R^g and R³⁶ are as defined in (8') above provided that where R^g is unsubstituted C₂₋₆ alkynylene, R³⁶ is as defined in (5'') hereinbefore);

10'') -R^hR³⁷ (wherein R^h and R³⁷ are as defined in (10') above provided that where R^h is unsubstituted C₂₋₆ alkenylene, R³⁷ is R³⁷ is a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group as (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group 5 which is substituted as described in (6') provided it carries at least one substituent selected from nitro, amino, C₁₋₄hydroxyalkoxy, oxo, cyanoC₁₋₄alkyl, cyclopropyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, C₁₋₄alkanoyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy, carboxamido, trifluoromethyl, or a group -(O-)_f(R^{b'})_gringD 10 (wherein f, g, R^{b'} and D are as defined above));

11'') -RⁱR³⁷ (wherein Rⁱ and R³⁷ are as defined in (11') above provided that where Rⁱ is unsubstituted C₂₋₆ alkynylene, R³⁷ is R³⁷ is a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group as (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group 15 which is substituted as described in (6') provided it carries at least one substituent selected from nitro, amino, C₁₋₄hydroxyalkoxy, oxo, cyanoC₁₋₄alkyl, cyclopropyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, C₁₋₄alkanoyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy, carboxamido, trifluoromethyl, or a group -(O-)_f(R^{b'})_gringD 20 (wherein f, g, R^{b'} and D are as defined above);

12'') -R^jX⁸R³⁷ (wherein R^j and R³⁷ are as defined in (12') above, and X⁸ is -C(O)-, -NR⁵⁰C(O)O- or -C(O)ONR⁵¹- (wherein R⁵⁰ and R⁵¹ are as defined in (12') above, or X⁸ is any other group listed in (12') above) and either R³⁷ is a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group as (linked via carbon or nitrogen) with 1-3 25 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group which is substituted as described in (6') provided it carries at least one substituent selected from nitro, amino, C₁₋₄hydroxyalkoxy, oxo, cyanoC₁₋₄alkyl, cyclopropyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, C₁₋₄alkanoyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, 30 di(C₁₋₄alkyl)aminoC₁₋₄alkoxy, carboxamido, trifluoromethyl, or a group -(O-)_f(R^{b'})_gringD

(wherein f, g, R^b and D are as defined above); or R^j is other than unsubstituted C₂-
6alkenylene;

13'')-R^kX⁹R³⁷ (wherein R^k and R³⁷ are as defined in (13') above, and X⁹ is -C(O)-,
-NR⁵⁵C(O)O- or -C(O)ONR⁵⁶-, (wherein R⁵⁵ and R⁵⁶ are as defined in (13') above, or X⁹ is
5 any other group listed in (13') above) and either R³⁷ is a pyridone group, a phenyl group or a
5-6-membered aromatic heterocyclic group as (linked via carbon or nitrogen) with 1-3
heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group
which is substituted as described in (6') provided it carries at least one substituent selected
from nitro, amino, C₁₋₄hydroxyalkoxy, oxo, cyanoC₁₋₄alkyl, cyclopropyl,

10 C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl,
C₁₋₄alkanoyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy,
di(C₁₋₄alkyl)aminoC₁₋₄alkoxy, carboxamido, trifluoromethyl, or a group -(-O-)_f(R^b)_gringD
(wherein f, g, R^b and D are as defined above); or R^k is other than unsubstituted C₂-6alkynylene

14'') -R^mX¹⁰R^{m'}R³⁷ (wherein R^m, R^{m'} and R³⁷ are as defined in (14') above, and X¹⁰ represents
15 -C(O)-, -NR⁶⁰C(O)O- or -C(O)ONR⁶¹-, (wherein R⁶⁰ and R⁶¹ are as defined in (14') above,
or where X¹⁰ is any other group listed in (14') above, and either R³⁷ is a pyridone group, a
phenyl group or a 5-6-membered aromatic heterocyclic group as (linked via carbon or
nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic
heterocyclic group which is substituted as described in (6') provided it carries at least one
20 substituent selected from nitro, amino, C₁₋₄hydroxyalkoxy, oxo, cyanoC₁₋₄alkyl, cyclopropyl,
C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl,
C₁₋₄alkanoyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy,
di(C₁₋₄alkyl)aminoC₁₋₄alkoxy, carboxamido, trifluoromethyl, or a group -(-O-)_f(R^b)_gringD
(wherein f, g, R^b and D are as defined above), or at least one of R^m or R^{m'} is other than
25 unsubstituted C₁₋₃alkylene);

15'') R³⁶ (where R³⁶ is as defined in (5'') hereinbefore);

16'') -RⁿX¹⁰R^{n'}R³⁶ (wherein Rⁿ, R^{n'} and R³⁶ are as defined in (16') above and X¹⁰ represents
-C(O)-, -NR⁶⁰C(O)O- or -C(O)ONR⁶¹-, (wherein R⁶⁰ and R⁶¹ are as defined in (14') above
or X¹⁰ is any of the other groups set out in (14') above and either R³⁶ is as defined in (5'')
30 hereinbefore) or at least one of Rⁿ or R^{n'} is other than unsubstituted C₁₋₃alkyl;

17'') -R^p X¹⁰-R^{p'}R³⁷ (wherein X¹⁰ is as defined in (14') above and R^p, R^{p'} and R³⁷ are as defined in (6') hereinbefore);

18'') C₂₋₅alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, 5 aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;

19'') C₂₋₅alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and 10 N,N-di(C₁₋₄alkyl)aminosulphonyl;

20'') -R^tX¹⁰R^{t'}R³⁶ (wherein X¹⁰ is as defined in (14') above and R³⁶ is as defined in (5') hereinbefore);

21'') -R^uX¹⁰R^{u'}R³⁶ (wherein X¹⁰ is as defined in (14') above and R³⁶ is as defined in (5') hereinbefore); and

15 22'') -R^v R⁶⁹(R^{v'})_q(X¹⁰)_rR⁷⁰(wherein X¹⁰ is as defined in (14') above, q' is 0 or 1, r is 0 or 1, and R⁶⁹ is a C₁₋₃alkylene group or a cyclic group selected from cyclopropyl, cyclobutyl, cyclopentylene, cyclohexylene or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkylene group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group 20 may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, i(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group 25 -(O-)_f(R^{b'})_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a cyclic group selected from C₃₋₆cycloalkyl, aryl or 5-6-membered saturated or unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from halo and C₁₋₄alkyl); and R⁷⁰ is hydrogen, C₁₋₃alkyl, or a cyclic group selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and a 5-6-membered 30 saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno,

C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl,

5 C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group -(O-)_f(C₁₋₄alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and D is a cyclic group selected from C₃₋₆cycloalkyl, aryl or 5-6-membered saturated or unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from halo and C₁₋₄alkyl);

10 and wherein R^a, R^b, R^{b'}, R^c, R^{c'}, R^d, R^e, Rⁱ, R^m, R^{m'} Rⁿ, R^{n'}, R^p', R^t', R^u', R^v and R^{v'} are independently selected from C₁₋₈alkylene groups optionally substituted by one or more substituents selected from hydroxy, halogeno, amino, R^f, R^h, R^j, R^p and R^t are independently selected from C₂₋₈alkenylene groups optionally substituted by one or more substituents selected from hydroxy, halogeno, amino, and R^t may

15 additionally be a bond; and

R^g, R^k and R^u are independently selected from by C₂₋₈alkynylene groups optionally substituted by one or more substituents selected from hydroxy, halogeno, amino, subject to the proviso set out above.

In many cases, it is preferred that where such groups include a bridging group R^a, R^b,

20 R^{b'}, R^c, R^{c'}, R^d, R^e, Rⁱ, R^m, R^{m'} Rⁿ, R^{n'}, R^p', R^t', R^u', R^v, R^{v'} R^f, R^h, R^j, R^p, R^t, R^g, R^k, or R^u, said bridging group carries a substituent as defined above, and in particular a hydroxy substituent, in order to block metabolism.

In particular, at least one of R¹, R², R³ or R⁴ is a group of formula X¹-R¹³ where R¹³ is a group as defined in (3''), (5''), (19'') or (22'').

25 When said group is a group of formula 3'', particularly suitable groups R²⁴ are cyclopropyl or any C₁₋₆ alkyl group substituted by cyclopropyl. Suitably in said groups, X³ is a group NR²⁹ where R²⁹ is as defined in 3' above and in particular is hydrogen.

When said group is a group of formula 5'', particularly suitable examples are compounds where R³⁶ is a saturated 7-membered heterocyclic ring or R³⁶ is a 5 or 6

30 membered heterocyclic ring such a a morpholine, piperidine or tetrahydropyridyl ring, which

-30-

carries at least one substituent selected from C₁₋₄alkanoyl such as acetyl, or -C(O)NR⁶⁵R⁶⁶, - (wherein R⁶⁵ and R⁶⁶ are as defined in (5') above and in particular are hydrogen.

When said group is a group of formula 19'', it is preferably an unsubstituted alkynyl group such as prop-2-ynyl.

5 When said group is a group of formula 22'' above, it is suitably a group in which R⁶⁹ is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, such as piperidinyl. Suitably R⁷⁰ is hydrogen or C₁₋₃alkyl such as methyl. Suitably also, X¹⁰ is oxygen. R^v and R^{v'} are suitably the same or different and are C₁₋₅alkylene groups in particular C₂₋₃alkylene groups.

10 In one embodiment, R¹, R², R³ or R⁴ is a member selected from the group consisting of hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, -NR¹¹R¹² (wherein R¹¹ and R¹², which may be the same or different, each represents hydrogen or C₁₋₃alkyl), or a group R¹³-X¹-(CH₂)_x wherein x is 0 to 3, X¹ represents -O-, -CH₂-, -OCO-, carbonyl, -S-, -SO-, -SO₂-, -NR¹⁴CO-, -CONR¹⁵-, -SO₂NR¹⁶-, -NR¹⁷SO₂- or -NR¹⁸- (wherein R¹⁴, R¹⁵, R¹⁶, 15 R¹⁷ and R¹⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹³ is selected from one of the following sixteen groups:

- 1) C₁₋₅alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino;
- 2) C₁₋₅alkylX²COR¹⁹ (wherein X² represents -O- or -NR²⁰- (wherein R²⁰ represents hydrogen, 20 C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁹ represents -NR²¹R²²- or -OR²³- (wherein R²¹, R²² and R²³ which may be the same or different each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl));
- 3) C₁₋₅alkylX³R²⁴ (wherein X³ represents -O-, -S-, -SO-, -SO₂-, -OCO-, -NR²⁵CO-, -CONR²⁶-, -SO₂NR²⁷-, -NR²⁸SO₂- or -NR²⁹- (wherein R²⁵, R²⁶, R²⁷, R²⁸ and R²⁹ each independently 25 represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁴ represents hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear one or two substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl,
- 30 C₁₋₄hydroxyalkyl and C₁₋₄alkoxy);

4) $C_{1-5}alkylX^4C_{1-5}alkylX^5R^{30}$ (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO₂-, -NR³¹CO-, -CONR³²-, -SO₂NR³³-, -NR³⁴SO₂- or -NR³⁵- (wherein R³¹, R³², R³³, R³⁴ and R³⁵ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁰ represents hydrogen or C₁₋₃alkyl);

5) $C_{1-5}alkylR^{36}$ (wherein R³⁶ is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl and C₁₋₄alkoxy);

6) $(CH_2)_qX^6R^{37}$ (wherein q is an integer from 0 to 5, X⁶ represents a direct bond, -O-, -S-, -SO₂-, -NR³⁸CO-, -CONR³⁹-, -SO₂NR⁴⁰-, -NR⁴¹SO₂- or -NR⁴²- (wherein R³⁸, R³⁹, R⁴⁰, R⁴¹ and R⁴² each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁷ is a phenyl group, a pyridone group or a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which phenyl, pyridone or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, amino, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄hydroxyalkoxy, C₁₋₄aminoalkyl, C₁₋₄alkylamino, carboxy, cyano, -CONR⁴³R⁴⁴ and -NR⁴⁵COR⁴⁶ (wherein R⁴³, R⁴⁴, R⁴⁵ and R⁴⁶, which may be the same or different, each represents hydrogen, C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl));

7) $C_{2-6}alkenylR^{36}$ (wherein R³⁶ is as defined in (5) above);

8) $C_{2-6}alkynylR^{36}$ (wherein R³⁶ is as defined in (5) above);

9) X^7R^{47} (wherein X⁷ is -SO₂-, -O- or -CONR⁴⁸R⁴⁹- (wherein R⁴⁸ and R⁴⁹, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R⁴⁷ represents C₁₋₅alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino) with the provisos that when X⁷ is -SO₂-, X¹ is -O-, when X⁷ is -O-, X¹ is carbonyl, when X⁷ is -CONR⁴⁸R⁴⁹-, X¹ is -O- or NR¹⁸ (wherein R⁴⁸, R⁴⁹ and R¹⁸ are as defined above);

10) $C_{2-6}alkenylR^{37}$ (wherein R³⁷ is as defined in (6) above);

11) $C_{2-6}alkynylR^{37}$ (wherein R³⁷ is as defined in (6) above);

12) $C_{2-6}alkenylX^8R^{37}$ (wherein X⁸ represents -O-, -S-, -SO₂-, -NR⁵⁰CO-, -CONR⁵¹-, -SO₂NR⁵²-, -NR⁵³SO₂- or -NR⁵⁴- (wherein R⁵⁰, R⁵¹, R⁵², R⁵³ and R⁵⁴ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁷ is as defined in (6) above);

13) $C_{2-6}\text{alkynyl}X^9R^{37}$ (wherein X^9 represents -O-, -S-, -SO-, -SO₂-, -NR⁵⁵CO-, -CONR⁵⁶-, -SO₂NR⁵⁷-, -NR⁵⁸SO₂- or -NR⁵⁹- (wherein R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸ and R⁵⁹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁷ is as defined in (6) above);

14) $C_{1-3}\text{alkyl}X^{10}C_{1-3}\text{alkyl}R^{37}$ (wherein X¹⁰ represents -O-, -S-, -SO-, -SO₂-, -NR⁶⁰CO-, -CONR⁶¹-, -SO₂NR⁶²-, -NR⁶³SO₂- or -NR⁶⁴- (wherein R⁶⁰, R⁶¹, R⁶², R⁶³ and R⁶⁴ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁷ is as defined in (6) above);

15) R³⁶ (wherein R³⁶ is as defined in (5) above); and

16) $C_{1-3}\text{alkyl}X^{10}C_{1-3}\text{alkyl}R^{36}$ (wherein X¹⁰ and R³⁶ are as defined in (5) above).

10 Suitably, R¹ and R⁴ are hydrogen.

 Suitably R² and R³ are other than hydrogen and in particular are a group of formula -X¹-R¹³ as defined above.

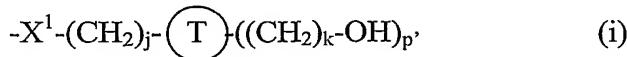
 Examples of preferred groups for R² include C₁₋₆alkoxy such as methoxy.

 The group R³ is suitably selected from hydrogen or C₁₋₆alkoxy. In other embodiments however, R³ is selected from

- (i) a group of formula -X¹-R^x-(OH)_p, where X¹ is as defined above, R^x is an alkylene, alkenylene or alkynylene chain, optionally interposed with a heteroatom or a heterocyclic ring and p' is 1 or 2;
- (ii) a group of formula R¹³-X²⁰-(CH₂)_x where R¹³ and x are as defined above and X²⁰ is a group -NR¹⁴C(O)-, -C(O)NR¹⁵- or -NR¹⁸- where R¹⁴, R¹⁵ and R¹⁸ are as defined above;
- (iii) a group of formula -X¹-R^y-NR^{zz}-R^{y'}-S-R^{y''} where X¹ is as defined above, R^y, R^{y'} and R^{y''} are independently selected from alkyl, alkenyl or alkynyl chains, and R^{zz} is hydrogen or alkyl, or R^{zz} and R^{y''} are joined together to form an optionally substituted nitrogen and sulphur containing ring; or
- (iv) a group of formula -X¹-R^x-(C₄₋₆cycloalkyl) where X¹ is as defined above and R^x is an alkylene, alkenylene or alkynylene chain, optionally interposed with a heteroatom.

 When R³ is a group of formula -X¹-R^x-(OH)_p, suitable examples of X¹ are -O-, -NR¹⁴C(O)-, -C(O)NR¹⁵- or -NR¹⁸- where R¹⁴, R¹⁵ and R¹⁸ are as defined above. In particular X¹ is -O-. Particular examples of R^x are C₂₋₆alkylene chains which is interposed by at least one heteroatom such as nitrogen, or a heterocyclic ring, in particular, a saturated 5-6membered heterocyclic ring. The ring suitably contains at least from one to three and preferably one

heteroatom which is suitably nitrogen. In particular, the heterocyclic ring is a saturated heterocyclic ring. The hydroxy groups may be attached to the alkylene portion of the group R^x or where present, the heterocyclic ring. In particular, these groups are groups of sub-formula (i)



where X^1 and p is as defined above, T is a 5 or 6 membered nitrogen containing ring, j is 2, 3, 4, or 5, and k is 0, 1, 2 or 3

Where the alkylene chain R^x is interposed with a nitrogen atom, it is suitably in the form or a group $-NR^{85}-$ where R^{85} is hydrogen or alkyl, in particular C_{1-3} alkyl.

Where R^3 is a group of formula $R^{13}-X^{20}-(CH_2)_x$, x is suitably 0. Preferred groups R^{13} are those set out below in respect of R^1 , R^2 and R^4 . Suitably R^{14} , R^{15} and R^{18} are hydrogen or C_{1-3} alkyl and preferably hydrogen.

Particular examples of groups of formula $-X^1-R^y-NR^{zz}-R^{y'}-S-R^{y''}$ for R^3 are groups where X^1 is $-O-$, $-NR^{14}C(O)-$, $-C(O)NR^{15}-$ or $-NR^{18}-$ where R^{14} , R^{15} and R^{18} are as defined above. In particular X^1 is $-O-$. Suitably R^y is a C_{2-6} alkylene group. Suitably $R^{y''}$ is a C_{2-3} alkylene group. Particular examples of $R^{y''}$ are C_{1-4} alkyl. Suitably R^z is hydrogen or C_{1-3} alkyl and in particular is hydrogen.

In one embodiment however, the group $-NR^{zz}-R^{y'}-S-R^{y''}$ is a thiomorpholine ring.

Where R^3 is a group of formula $-X^1-R^{x'}-(C_{4-6}\text{cycloalkyl})$, X^1 is suitably $-O-$, $-NR^{14}C(O)-$, $-C(O)NR^{15}-$ or $-NR^{18}-$ where R^{14} , R^{15} and R^{18} are as defined above. In particular X^1 is $-O-$. Particular examples of $R^{x'}$ are C_{2-5} alkylene groups which suitably include at least one heteroatom in particular a group $-NR^{85}-$ where R^{85} is as defined above. Suitably the $C_{4-6}\text{cycloalkyl}$ group is cyclopentyl.

A further preferred group for R^2 or R^3 is 3-morpholinopropoxy.

Suitably at least one of R^2 or R^3 is a group $-X^1-R^{13}$ where X^1 is as defined above and R^{13} is any of the groups defined in any one of the twenty two group (1'') - (22'') as set out above. Preferably R^3 is said group. In this case, the other group R^2 and R^3 may be any of the 5 groups defined above for R^1 , R^2 , R^3 or R^4 . Preferably however said other group is a small group such as hydrogen or C_{1-6} alkoxy such as methoxy.

In one embodiment R¹ and R⁴ are each hydrogen and R² and R³ are independently selected from C₁₋₄alkoxy or a group of the formula -(CH₂)_x-X¹-R¹³ wherein x is 0 and X¹ is selected from -O-, -NR¹⁸- or -NR¹⁵C(O)- (wherein R¹⁵ and R¹⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹³ is selected from one of the following 5 groups:

- 1) C₁₋₅alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, oxiranyl, fluoro, chloro, bromo and amino;
- 2) -R^bX³R²⁴ wherein R^b, X³ and R²⁴ are as defined above;
- 3) -R^dR³⁶ wherein R^d and R³⁶ are as defined above; and
- 4) -RⁿX¹⁰R^{n'}R³⁶ wherein Rⁿ, X¹⁰, R^{n'} and R³⁶ are as defined above;

Particularly, R¹ and R⁴ are each hydrogen; R² is C₁₋₄alkoxy and R³ is selected from a group of the formula -(CH₂)_x-X¹-R¹³ wherein x is 0 and X¹ is selected from -O-, -NR¹⁸- or -NR¹⁵C(O)- (wherein R¹⁵ and R¹⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹³ is selected from one of the following groups:

- 1) C₁₋₅alkyl substituted with cyano;
- 2) -R^bX³R²⁴ wherein R²⁴ is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl or a 5-6 membered saturated heterocyclic group, X³ is -NR²⁹- (wherein R²⁹ is as defined above) and R^b is as defined above;
- 3) -R^dR³⁶ wherein R³⁶ is a saturated heterocyclic group with 1 or 2 heteroatoms independently selected from O, S and N which group may bear 1 or 2 substituents as defined above and R^d is as defined above; and
- 4) -RⁿX¹⁰R^{n'}R³⁶ wherein R³⁶ is a saturated heterocyclic group with 1 or 2 heteroatoms independently selected from O, S and N which group may bear 1 or 2 substituents as defined above, X¹⁰ is -CO- and Rⁿ, and R^{n'} are as defined above;

In another embodiment, R¹, and R⁴ are both hydrogen, R² is methoxy and R³ is independently selected from pyrrolidin-1-ylpropoxy, pyrrolidin-1-ylpropylamino, morpholinopropoxy, piperidinopropoxy, thiomorpholinopropoxy, 1-oxo-thiomorpholinopropoxy, 1,1-dioxo-thiomorpholinopropoxy, cyclopropylaminopropoxy, azetidin-1-ylacetymethoxy, pyrrolidin-1-ylacetymethoxy, 4-methylmorpholin-2-ylmethoxy, 2,6-dimethylmorpholinopropoxy, 3,5-dimethylmorpholinopropoxy, 2,6-dimethylpiperidin-1-ylpropoxy, 4-methoxyethylpiperazin-1-ylpropoxy,

4-acetyl piperazin-1-ylpropoxy, 3-methylsulphonylpyrrolidin-1-ylpropoxy, 4-ethylsulphonylpiperazin-1-ylpropoxy, imidazol-1-ylethoxy, 1,1-dioxo-tetrahydrothiophen3-yl(N-methylamino)propoxy, 3-hydroxypiperidin-1-ylpropoxy, N,N-di-(hydroxyethyl)aminopropoxy and hydroxyethoxyethoxy.

5

In yet a further embodiment, both R^2 and R^3 are C_{1-6} alkoxy and are preferably methoxy.

Preferably, R^5 is cyano.

Suitable groups Y include oxygen or -NH- and most preferably are -NH-.

In particular, in the compound of formula (I), (IA) or (IB), n is 0.

Suitably R^8 is a divalent phenyl. Preferably X is arranged on R^8 is in the para position.

Suitably X is oxygen or -NH- and most preferably oxygen.

Suitably m is 0.

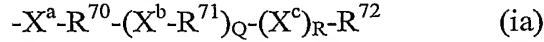
Examples of optional substituents for heterocyclic groups R^9 or aryl, carbocyclic or 10 heterocyclic groups R^{10} as well as substituents for alkyl group R^{110} in R^8 include one or more groups selected from hydroxy; halo; nitro; cyano; carboxy; C_{1-6} alkoxy; C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{2-6} alkenyloxy; C_{2-6} alkynyloxy; C_{3-6} cycloalkyl; amino; mono- or di- C_{1-6} alkyl amino; heterocyclyl optionally substituted with C_{1-6} alkyl or oxo; $C(O)R^{aa}$; $C(O)OR^{aa}$; $S(O)_dR^{aa}$; $NR^{aa}C(O)R^{bb}$; $C(O)NR^{aa}S(O)_dR^{bb}$; $C(O)NR^{aa}R^{bb}$; $NR^{aa}C(O)NR^{bb}R^{cc}$; 15 $NR^{aa}S(O)_dR^{bb}$ or $N(S(O)_dR^{bb})S(O)_dR^{cc}$ where d is 0, 1 or 2 and R^{aa} , R^{bb} and R^{cc} are independently selected from hydrogen, C_{1-6} alkyl, aryl, C_{3-6} cycloalkyl or heterocyclyl, and wherein any alkyl, alkenyl or alkynyl group or moiety contained within the substituent on R^{10} may themselves be optionally substituted with one or more groups selected from hydroxy; cyano; nitro; halo; carboxy; carboalkoxy of 2-7 carbon atoms; C_{3-6} cycloalkyl; heterocyclyl 20 optionally substituted with C_{1-6} alkyl or oxo; $C(O)R^{dd}$; $C(O)OR^{dd}$ $NR^{dd}R^{ee}$; $S(O)_eR^{dd}$; $NR^{dd}C(O)R^{ee}$; $C(O)NR^{dd}R^{ee}$; $NR^{dd}C(O)NR^{ee}R^{ff}$; or $NR^{dd}S(O)_eR^{ee}$ where e is 0, 1 or 2 and R^{dd} , R^{ee} and R^{ff} are independently selected from hydrogen or C_{1-6} alkyl optionally substituted with one or more groups selected from hydroxy; cyano; nitro; halo; carboxy; carboalkoxy of 2-7 carbon atoms; C_{3-6} cycloalkyl; heterocyclyl optionally substituted with C_{1-6} alkyl or oxo; 25 $C(O)R^{gg}$; $C(O)OR^{gg}$; $NR^{gg}R^{hh}$; $S(O)_eR^{gg}$; $NR^{hh}C(O)R^{gg}$; $C(O)NR^{gg}R^{hh}$; $NR^{gg}C(O)NR^{hh}R^{ii}$;

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or $NR^{gg}S(O)_eR^{hh}$ where e is as defined above and R^{gg} , R^{hh} and R^{ii} are independently selected from hydrogen, C₁₋₆alkyl or heterocyclyl.

In some embodiments, the level of substitution on the group R¹⁰ is complex.

Thus, for example, a substituent may comprise a substituted alkyl chain which is 5 optionally interposed with heteroatoms such as groups of sub-formula (ia)

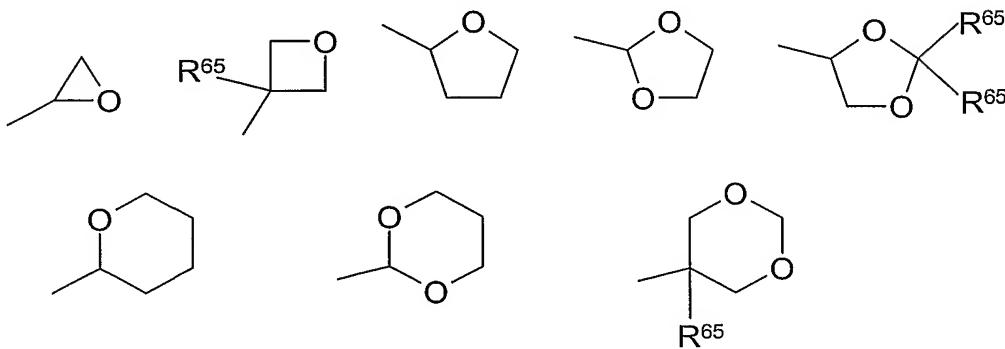


where X^a, X^b and X^c are independently selected from any of the groups listed above for X¹,

R⁷⁰ and R⁷¹ are independently selected from C₁₋₆alkylene, C₂₋₆alkenylene or 10 C₂₋₆alkynylene groups any of which may be optionally substituted with hydroxy; cyano; nitro; halo; carboxy; carboalkoxy of 2-7 carbon atoms or C₃₋₆cycloalkyl; R⁷² is hydrogen or an C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl group any of which may be 15 optionally substituted with hydroxy; cyano, nitro, halo, carboxy, C₃₋₆cycloalkyl and in particular cyclopropyl, or an optionally substituted heterocyclic group, in particular a group as defined above for R³⁶, and Q and R are independently 0 or 1.

In some embodiments, R¹⁰ is a heterocyclic ring containing one or 2 oxygen atoms.

Examples of heterocyclic rings R¹⁰ include 3- 7 membered rings, up to two of which may be oxygen atoms. Such groups include:



20 where each R⁶⁵ is independently selected from hydrogen or C₁₋₆alkyl and especially methyl.

Other examples of heterocyclic groups R¹⁰ include pyridyl, thiazolyl, pyrazinyl, pyrimidinyl, oxadiazole.

Particular examples of groups R¹⁰ include a divalent phenyl, pyridyl or C₃₋₈cycloalkyl. Most preferably however, R¹⁰ is an optionally substituted phenylene. R⁹ is preferably a group 25 selected from C₁₋₂ alkylene, or a divalent C₃₋₄ cycloalkyl, pyridyl, pyrrolidinyl or phenyl.

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Suitable further substituents for R⁹ and R¹⁰ include those listed above for pyridyl, pyrimidinyl and phenyl groups R⁸.

In a preferred embodiment R⁹ and R¹⁰ are both phenylene; Y is -NH and X is oxygen; and n, m and p are all 0. A particularly preferred substituent on R¹⁰ is fluoro.

5 Preferably R⁶ is hydrogen,

Suitable examples of variables within sub-formula (i) defined above are as follows:

X¹² is suitably -O-;

10 R⁷⁵ is suitably C₁₋₆alkylene and preferably the group -C(R^A R^B) where R^A and R^B are each independently selected from C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl and halo, are most preferably both either C₁ alkyl or fluoro. R⁷⁶ and R⁷⁷ are suitably the same or different and are preferably independently selected from C₁₋₆alkylene and in particular methylene groups and a direct bond. Most preferably R⁷⁷ is a direct bond.

15 X¹³ is preferably the group -CONR⁷⁹- or -NR⁷⁸C(O)-, most preferably the group -CONR⁷⁹-, where R⁷⁸ and R⁷⁹ are selected from hydrogen or C₁₋₃ alkyl and are more preferably hydrogen;

X¹⁴ is suitably -C(O)-, -CONR⁷⁹-, where R⁷⁸ and R⁷⁹ are selected from hydrogen or C₁₋₃ alkyl and are preferably hydrogen, or a direct bond;

s, s', q and p are all preferably 0.

Where Z is a group of sub-formula (i), a particularly preferred group is selected from

20 -O-C(CH₃)₂-CONR⁷⁹-;
 -O-C(F)₂-;
 -O-C(CH₃)₂-CONR⁷⁹-CH₂-CONR⁷⁹-;
 -O-C(CH₃)₂-CONR⁷⁹-CH₂-CONR⁷⁹-(CH₂)₂-NR⁸²-;
 -O-C(F)₂-CONR⁷⁹-;
 25 -O-C(F)₂-CONR⁷⁹-CH₂-CONR⁷⁹-;
 -O-C(CH₃)₂-CONR⁷⁹-CH₂-NR⁸²-;
 -O-C(CH₃)₂-CONR⁷⁹-(CH₂)₂-SO₂-;
 -O-C(CH₃)₂-CONR⁷⁹-(CH₂)₂-S-; and
 -O-C(CH₃)₂-CONR⁷⁹-(CH₂)₂-O-

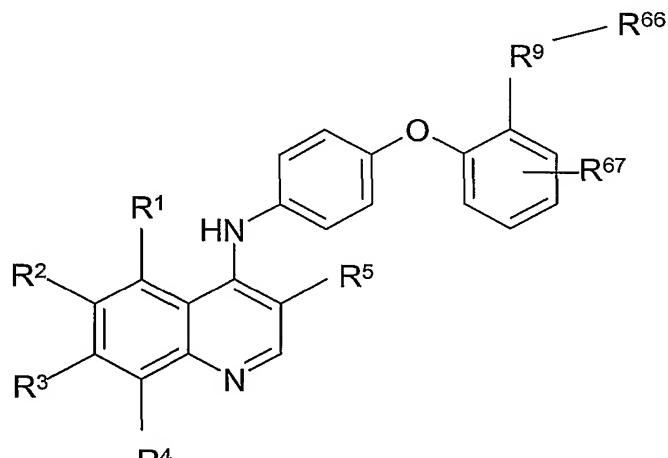
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where R^{79} , R^{82} are preferably as hereinbefore defined and preferably are methyl or hydrogen, most preferably hydrogen. Alternatively Z is preferably a direct bond.

Examples of suitable heterocyclic groups R^9 are 5- or 6-membered aromatic or non-aromatic rings which contain up to 4 and preferably up to 3 heteroatoms. A particular 5 example of a non-aromatic group R^9 is piperazino or morpholine or piperidine linked via carbon or nitrogen but preferably by nitrogen atoms whilst an example of an aromatic group is oxadiazole.

Where Z is a group of sub-formula (i), R^9 may be substituted by a simple C_{1-6} alkyl group such as methyl. However, where Z is a direct bond, more complex substituents are 10 required to be present on the ring R^9 . In such instances, at least one group X^{17} , X^{17} or X^{18} , and preferably at least X^{18} , in the group of sub-formula (ii) is other than a direct bond. Preferably, at least one such group, and most preferably X^{18} is $-S-$, $-S(O)-$ or $-S(O)_2-$.

Thus a sub-group of compounds of formula (I) are compounds of formula (IC)



15

(IC)

where R^1 , R^2 , R^3 , R^4 , R^5 and R^9 are as defined above, R^{66} is a group of sub-formula (ii) as defined above where at least X^{18} is other than a direct bond; and R^{67} is selected from hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxyethyl of 2-7 carbon atoms, alkanoyloxyethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy,

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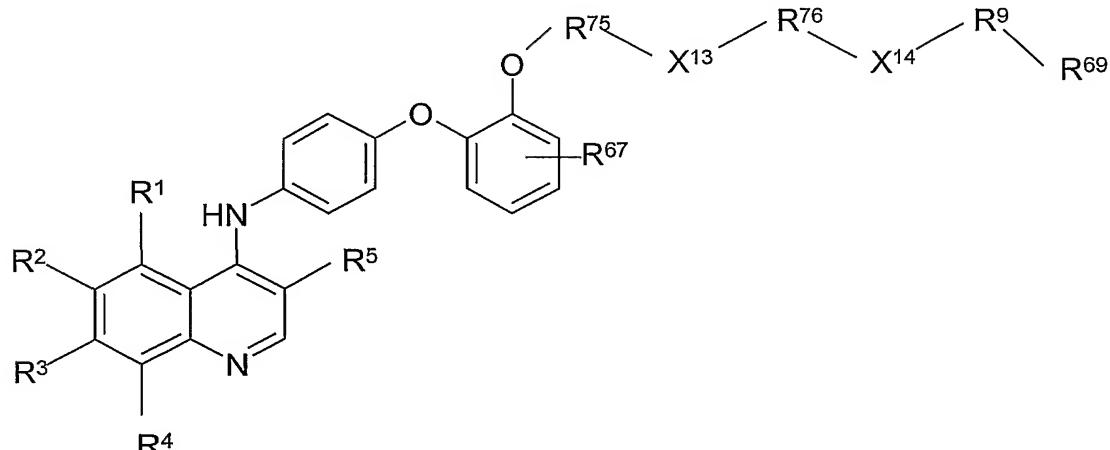
carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino.

5 Suitably R⁶⁶ is a C₁₋₆ alkylthioC₁₋₆alkyl group -CH₂SCH₃ or a sulphoxide derivative thereof.

Preferably R⁶⁷ is hydrogen.

Alternatively, in another embodiment, the compounds of formula (I) are compounds of formula (ID)

10

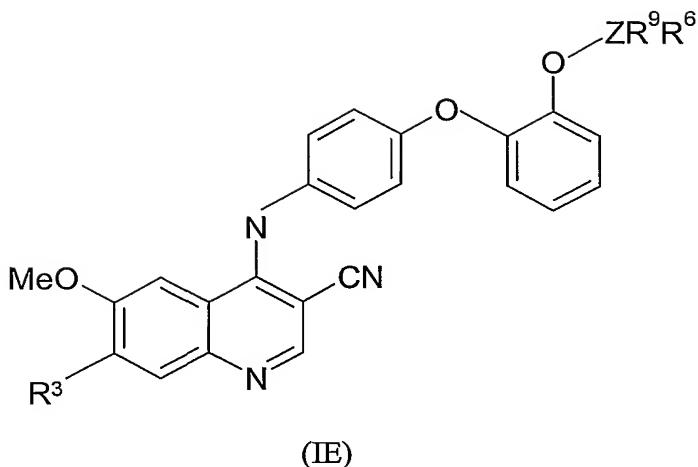


(ID)

where R¹, R², R³, R⁴, R⁵ and R⁹ are as defined above in relation to formula (I), R⁶⁷ is as defined above in relation to formula (IC), R⁷⁵, R⁷⁶, X¹³ and X¹⁴ are as defined above in 15 relation to sub-formula (i), and R⁶⁹ is a group of sub-formula (ii) as defined above but in particular is C₁₋₆alkyl.

Particularly preferred compounds according to the invention are compounds of formula (IE)

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or a pharmaceutically acceptable salt, prodrug or solvate thereof; and wherein R^3 , Z , R^9 and
 5 R^6 are selected from the following groups:

- i) R^3 is $-OCH_3$, Z is the group $-O-C(CH_3)_2-CONH-CH_2-CONH-$, the group R^9-R^6 is $-C_2H_5$;
- ii) R^3 is $-OCH_3$, Z is the group $-O-C(CH_3)_2-CONH-CH_2-CONH-$, the group R^9-R^6 is cyclobutyl;
- 10 iii) R^3 is H, Z is the group $-O-C(CH_3)_2-CONH-CH_2-CONH-$, the group R^9-R^6 is CH_3 ;
- iv) R^3 is H, Z is the group $-O-C(CH_3)_2-CONH-CH_2-CONH-$, the group R^9-R^6 is CH_3 ;
- v) R^3 is $-OCH_3$, Z is the group $-O-C(CH_3)_2-CONH-CH_2-CON(CH_3)-$, the group R^9-R^6 is $-CH_3$;
- 15 vi) R^3 is $-OCH_3$, Z is the group $-O-C(CH_3)_2-CONH-CH_2-CONH-$, the group R^9-R^6 is cyclopropyl;
- vii) R^3 is $-OCH_3$, Z is the group $-O-C(CH_3)_2-CONH-CH_2-CONH-CH_2$, the group R^9-R^6 is cyclopropyl;
- viii) R^3 is $-OCH_3$, Z is the group $-O-C(CH_3)_2-CONH-CH_2-CONH-CH_2$, the group R^9-R^6 is CH_3 ;
- 20 ix) R^3 is $-NHCH_3$, Z is the group $-O-C(CH_3)_2-CONH-$ the group R^9-R^6 is CH_3 ;
- x) R^3 is $-OCH_3$, Z is the group $-O-C(CH_3)_2-(CH_2)_2-$, the group R^9-R^6 is pyridine;
- xi) R^3 is $-NHCH_3$, Z is the group $-O-C(CH_3)_2-CONH-$, the group R^9-R^6 is cyclopropyl; and

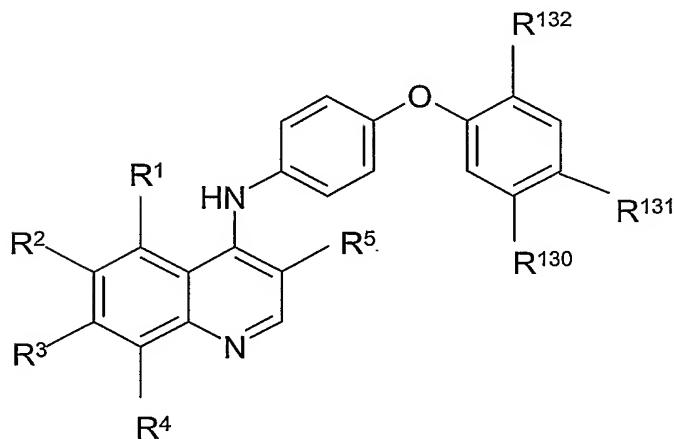
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xii) R^3 is $-OCH_3$, Z is the group $-O-C(CH_3)_2-CONH-CH_2-CONH-(CH_2)_2-N(CH_3)-$, the group R^9-R^6 is $-CH_3$; and

xiii) R^3 is 3-(1-morpholino)propoxy, Z is the group $-O-C(CH_3)-CONH-$, the group R^9-R^6 is $-(CH_2)_2OH$

5

A further group of compounds according to the invention are compounds of formula (IF)



(IF)

10

wherein

R^{130} is a group of formula (i) as hereinbefore defined and preferably is selected from $-NR^{78}C(O)-R^9-R^6$, $-NR^{82}-R^9-R^6$; and C_{1-4} alkoxy; hydrogen or halo, particularly fluoro, where R^{78} , R^{82} , R^9 and R^6 are as hereinbefore defined;

15

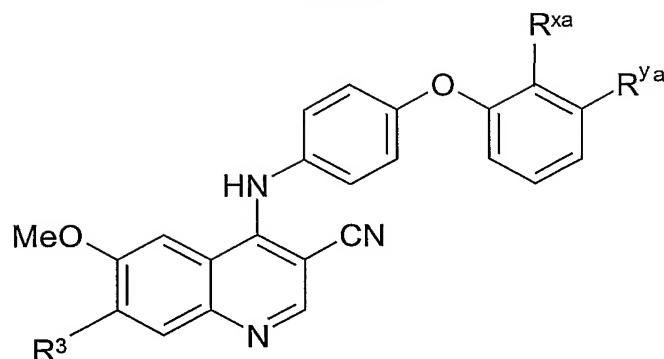
 R^{131} is a hydrogen or halo, particularly fluoro; and R^{132} is a C_{1-4} alkoxy

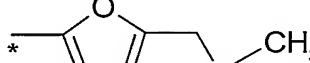
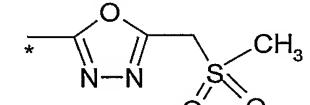
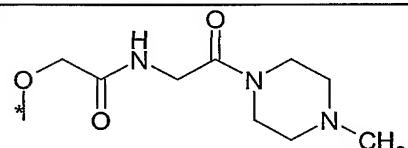
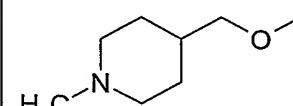
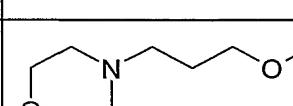
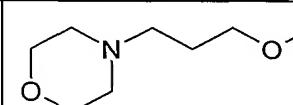
Particular examples of compounds according to the invention are listed in Tables 1 to 9 below, where * denotes the point of attachment.

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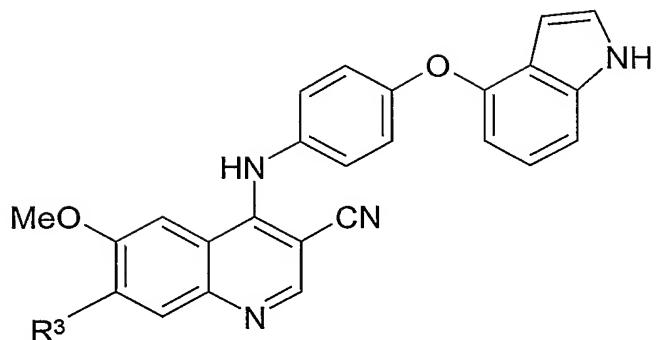
Table 1



Compd No	R ³	R ^{x a}	R ^{y a}
1	OCH ₃	* 	H
2	OCH ₃	* 	H
3	OCH ₃	* 	H
4	OCH ₃	OCH ₂ CH(OH)CH ₂ (N-morpholine)	H
5	OCH ₃	OCH ₂ CH(OH)CH ₂ (N-piperidine)	H
6	OCH ₃	OC(CH ₃) ₂ C(O)NHCH ₃	H
7	* 	OC(CH ₃) ₂ C(O)NHCH ₃	H
8	* 	OC(CH ₃) ₂ C(O)NHCH ₃	H
9	OCH ₃	OCH ₂ C(O)N(CH ₃)CH ₂ C(O)-OCH ₃	H
10	* 	H	C(O)NH-cyclopropyl

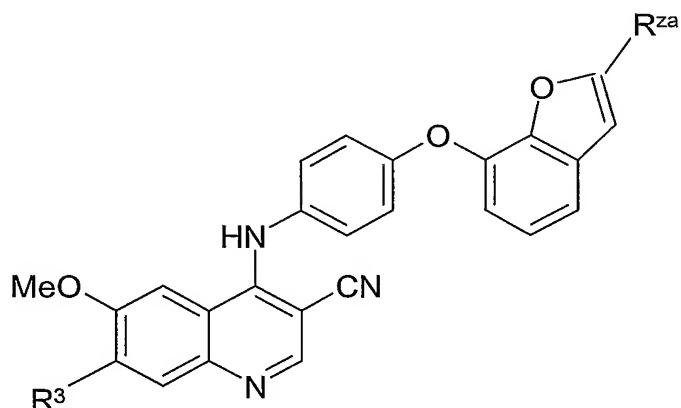
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Table 2



Compd No	R ³
11	OCH ₃

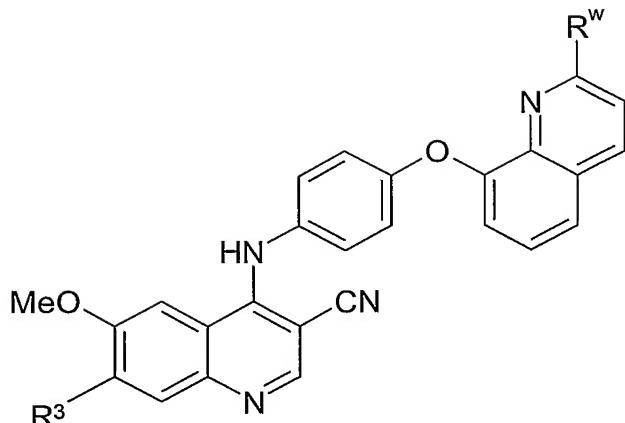
Table 3



Compd No	\mathbf{R}^3	\mathbf{R}^{za}
12	OCH_3	$\text{C}(\text{O})-\text{NCH}_3$
13	OCH_3	$\text{C}(\text{O})-\text{N-cyclopropyl}$

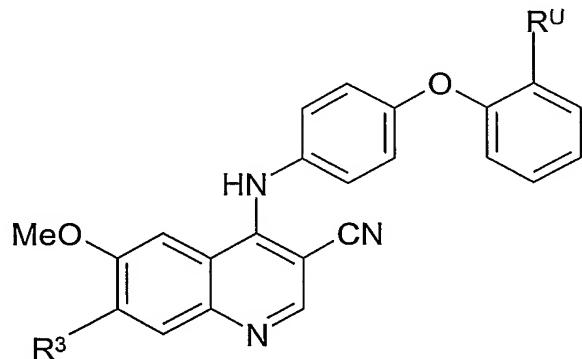
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Table 4

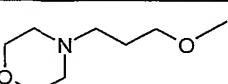


Compd No.	R ³	R ^W
14	OCH ₃	C(O)NC(CH ₃) ₂
15	OCH ₃	C(O)-N-cyclopropyl

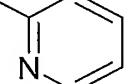
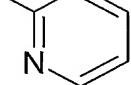
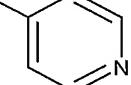
Table 5



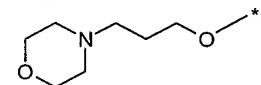
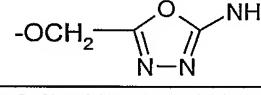
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Compd No	R ³	R ^U
15A	OCH ₃	-OC(CH ₃) ₂ C(O)NH-cyclopropyl
16	 *	-OC(CH ₃) ₂ C(O)NH-cyclopropyl
17	OCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₃ - 
18	OCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₂ - 

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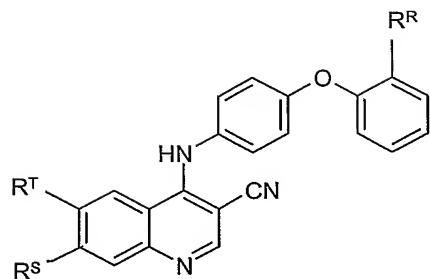
Compd No	R ³	R ^U
19	OCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₂ -N 
20	OCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₃ -N 
21	OCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₃ -N 
22	OCH ₃	-OC(CH ₃) ₂ C(O)NHCH ₂ C(O)NH-cyclopropyl
23	OCH ₃	-OC(CH ₃) ₂ C(O)NHCH ₂ C(O)N-CH ₂ -cyclopropyl
24	OCH ₃	-OC(CH ₃) ₂ C(O)NHCH ₂ C(O)NHCH ₃
25	OCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₂ N(CH ₃) ₂
26	NCH ₃	-OC(CH ₃) ₂ C(O)NHCH ₃
27	OCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₂ - 
28	OCH ₃	-OCH ₂ C(O)N(CH ₃)(CH ₂) ₂ - 
29	OCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₂ - 
30	OCH ₃	-OC(F) ₂ C(O)NHCH ₃
31	OCH ₃	-OC(F) ₂ C(O)NH-cyclopropyl
32	NCH ₃	-OC(CH ₃) ₂ C(O)NHCH ₂ C(O)NHCH ₃
33	NCH ₃	-OC(CH ₃) ₂ C(O)NHCH ₂ C(O)NH-cyclopropyl
34	OCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₂ -N 
35	OCH ₃	-OC(CH ₃) ₂ C(O)NHCH ₂ C(O)-NH(CH ₂) ₂ N(CH ₃) ₂
36	OCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₂ NHC ₂ H ₅
37	OCH ₃	-OC(CH ₃) ₂ C(O)NHCH ₂ C(O)NHC ₂ H ₅
38	OCH ₃	-OC(CH ₃) ₂ C(O)NHCH ₂ C(O)NH-cyclobutyl
39	H	OC(CH ₃) ₂ C(O)NH CH ₃
40	H	-OC(CH ₃) ₂ C(O)NHCH ₂ C(O)NHCH ₃
41	OCH ₃	-OC(F) ₂ C(O)NHCH ₂ C(O)NHCH ₃

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Compd No	R ³	R ^U
42	OCH ₃	-OC(F) ₂ C(O)NHCH ₂ C(O)NH-cyclopropyl
43	OCH ₃	-OC(CH ₃) ₂ C(O)NHCH ₂ C(O)NHC(CH ₃) ₂
44	OCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₂ SO ₂ CH ₃
45	OCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₂ SCH ₃
46	OCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₂ - 
47	NCH ₃	-OC(CH ₃) ₂ C(O)NHCH ₂ C(O)NHC ₂ H ₅
48	NCH ₃	-OC(CH ₃) ₂ C(O)NH-cyclopropyl
49	NCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₂ - 
50	OCH ₃	-OC(CH ₃) ₂ C(O)NH(CH ₂) ₂ OH
51		-OC(CH ₃) ₂ C(O)NH(CH ₂) ₂ OH
52	OCH ₃	-OC(CH ₃) ₂ C(O)NH ₂
52 A	OCH ₃	-OCH ₂ C(O)NH(CH ₂) ₂ - 
52 B	OCH ₃	-OCH ₂ C(O)NH(CH ₂) ₂ - 
52 C	OCH ₃	-OCH ₂ - 
52D	NHC(O)CH ₃	OCH(CH ₃) ₂ C(O)NHCH ₂ C(O)NHCH ₃

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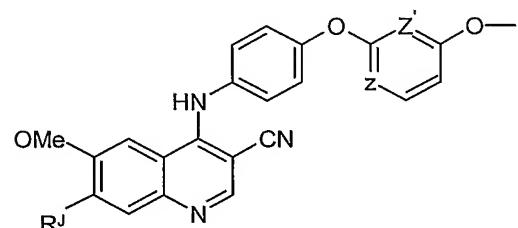
Table 6



Compd No.	R ^T	R ^S	R ^R
53	H	NCH ₃	-OC(CH ₃) ₂ C(O)NHCH ₃
54	NC(O)CH ₃	OCH ₃	-OC(CH ₃) ₂ C(O)NH-cyclopropyl

5

Table 7



10

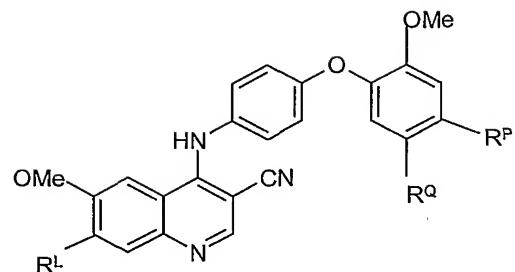
Compd No.	R ^J	Z	Z'
55		N	H
56	OCH ₃	<u>N</u>	H
57		H	N

15

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Table 8

5



Compd No.	$\mathbf{R}^{\mathbf{L}}$	$\mathbf{R}^{\mathbf{P}}$	$\mathbf{R}^{\mathbf{Q}}$
58		H	-NHC(O)CH ₃
59	OCH ₃	<u>H</u>	-NHC ₂ H ₅
60		H	-NHC ₂ H ₅
61		H	OCH ₃
62		F	H
63	OCH ₃	<u>H</u>	F
64		H	F

10

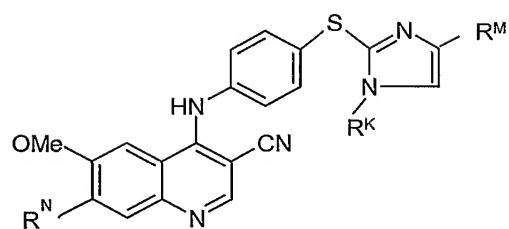
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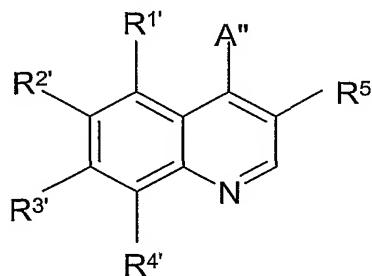
Table 9



10

Compd No.	R ^N	R ^M	R ^K
65	OCH ₃	-CO ₂ Et	-C ₂ H ₅
66		-CO ₂ Et	-C ₂ H ₅
67	OCH ₃	-C(O)OCH ₃	-C ₂ H ₅
68	OCH ₃	-C(O)O(CH ₂) ₂ CH ₃	-C ₂ H ₅

Compounds of formula (I) or (IA) are suitably prepared by reacting a compound of formula (II)

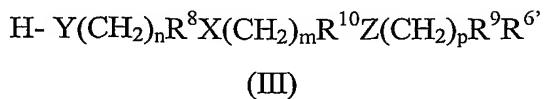


15

(II)

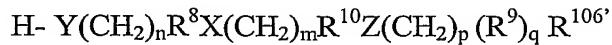
where R^{1'}, R^{2'}, R^{3'}, R^{4'} represent R¹, R², R³ and R⁴ respectively as defined in relation to formula (I) or a precursor thereof, R⁵ is as defined in relation to formula (I) and A'' is a leaving group, with a compound of formula (III)

20



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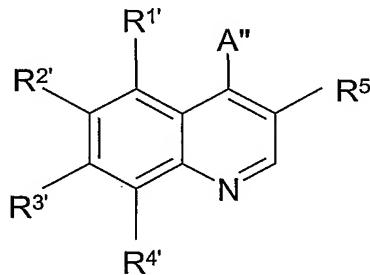
where $Y, n, R^8, X, m, R^{10}, Z, p$ and R^9 are as defined in relation to formula (I), and $R^{6'}$ is a group R^6 as defined in relation to formula (I) or a precursor thereof; or with a compound of formula (IV)



5

where $Y, n, R^8, X, m, R^{10}, Z, p, q$ and R^9 are as defined in relation to formula (IA) and $R^{106'}$ is a group R^{106} as defined in relation to formula (IA) or a precursor thereof; and thereafter if necessary or desired converting precursor groups $R^{1'}, R^{2'}, R^{3'}, R^{4'}, R^{6'}$ and $R^{106'}$ to groups of formula R^1, R^2, R^3, R^4, R^6 and R^{106} respectively, or converting a group R^1, R^2, R^3, R^4, R^6 and R^{106} to a different such group.

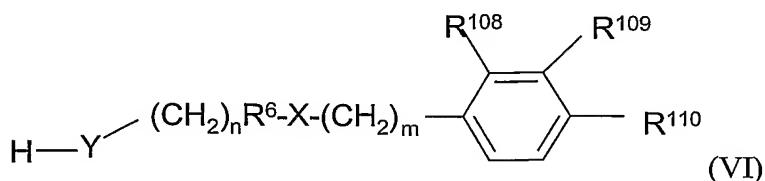
10 Alternatively compounds of formula (IB) are suitably prepared by reacting a compound of formula (V)



15

(V)

where $R^{1'}, R^{2'}, R^{3'}, R^{4'}$ represent R^1, R^2, R^3 and R^4 respectively as defined in relation to formula (IB) or a precursor thereof, R^5 is as defined in relation to formula (IB) and A'' is a leaving group, with a compound of formula (VI)



20

where $Y, n, R^6, X, m, R^{108}, R^{109}$ and R^{110} are as defined in relation to formula (IB), and thereafter if necessary or desired converting precursor groups $R^{1'}, R^{2'}, R^{3'}$ and $R^{4'}$ to groups of formula R^1, R^2, R^3 and R^4 respectively, or converting a group R^1, R^2, R^3 and R^4 to a different such group.

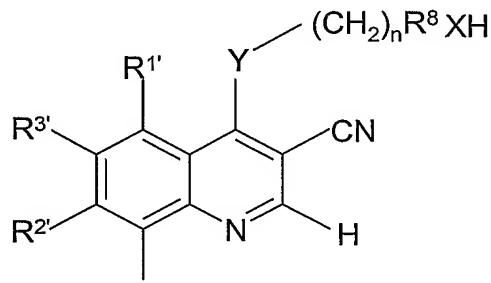
Suitable leaving groups for A" include halogen such as bromo or chloro, or a mesylate or tosylate group or a substituted phenoxy group.

The reaction is suitably carried out in an organic solvent such as an alcohol for example propanol or cyclohexanol at elevated temperatures, for example of from 50 to 150°C, 5 for example at about 105°C.

Conversion reactions in which precursor groups R^{1'}, R^{2'}, R^{3'}, R^{4'} are converted to groups of formula R¹, R², R³ and R⁴ respectively, or groups R^{1'}, R^{2'}, R^{3'} and R^{4'} are converted to different such group can be carried out using conventional chemistry as outlined hereinafter. Particular precursor groups R^{1'}, R^{2'}, R^{3'}, R^{4'} are groups of formula R^{13'}-X¹-(CH₂)_x 10 wherein x and X¹ are as defined herein, and R^{13'} is C₁₋₅alkyl which is substituted with halo other than fluoro, and in particular chloro or bromo. The chloro or bromo group may readily be converted into many other groups R¹³ as defined in relation to formula (I).

Similarly conversion reactions involving groups R⁶ or R¹⁰⁶ may be effected using conventional chemistry. For example substituent groups on a group R¹⁰ within the group R⁶ 15 or R¹⁰⁶ may be changed, for example by changing acids to esters or amides etc.

Alternatively, compounds of formula (I) or (IA) are prepared by reacting a compound of formula (VII)

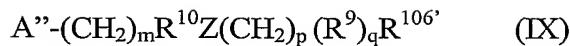


(VII)

20 where R^{1'}, R^{2'}, R^{3'}, R^{4'} are as defined in relation to formula (ID) R⁸, X, Y and n are as defined in relation to formula (I) or formula (IA), with a compound of formula (VIII)



25 where m, R¹⁰, Z, p and R⁹ are as defined in relation to formula (I), R^{6'} is as defined in relation to formula (III) and A" is a leaving group; or with a compound of formula (IX)

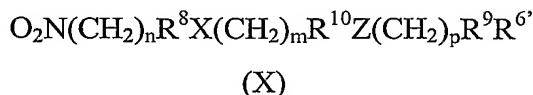


where m, R¹⁰, Z, p, q, and R⁹ are as defined in relation to formula (IA) and R¹⁰⁶ is a group 5 R¹⁰⁶ as defined in relation to formula (IA) or a precursor thereof and A'' is a leaving group; and thereafter if necessary or desired converting precursor groups R^{1'}, R^{2'}, R^{3'}, R^{4'}, R^{6'} and R^{106'} to groups of formula R¹, R², R³, R⁴ and R⁶ respectively, or converting a group R¹, R², R³, R⁴ and R⁶ to a different such group. Suitable leaving groups for A'' include halogen such a bromo or chloro, or a mesylate or tosylate group.

10 The reaction is suitably carried out in an organic solvent such as DMF at elevated temperatures, for example of from 40 to 120°C, for example at about 80°C. Conversion reactions are conventional and can be derived from literature information.

For example, where Y is NH, compounds of formula (III) are suitably prepared by reduction of a compound of formula (X)

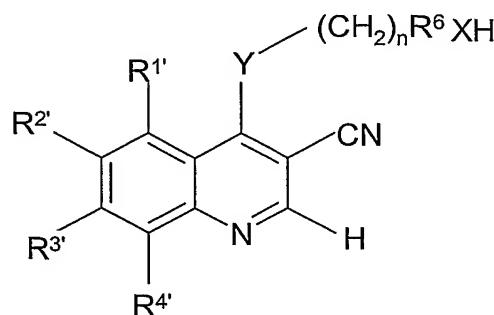
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where X, R⁸, R⁹, R¹⁰, Z, R^{6'} m, p and n are as defined above. It may be convenient to convert precursor groups R^{6'} to groups R⁶ or groups R⁶ to other such groups at the level of compound 20 of formula (X) or (III) using conventional chemistry. A similar process can be used to make compounds of formula (IV).

Compounds of formula (VII) are also known compounds or they can be prepared from known compounds by conventional methods.

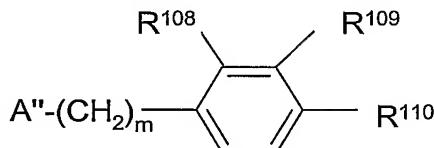
Alternatively, compounds of formula (IB) are prepared by reacting a compound of 25 formula (XI)



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(XI)

where $R^{1'}, R^{2'}, R^{3'}, R^{4'}$ are as defined in relation to formula (IB) R^6 , X, Y and n are as defined in relation to formula (I), with a compound of formula (XII)



5

(XII)

where m, R^{108} , R^{109} and R^{110} are as defined in relation to formula (IB), and A'' is a leaving group; and thereafter if necessary or desired converting precursor groups $R^{1'}, R^{2'}, R^{3'}$ and $R^{4'}$ to groups of formula R^1 , R^2 , R^3 and R^4 respectively, or converting a group R^1 , R^2 , R^3 and R^4 to a different such group. Suitable leaving groups for A'' include halogen such a bromo or 10 chloro, or a mesylate or tosylate group.

The reaction is suitably carried out in an organic solvent such as DMF at elevated temperatures, for example of from 40 to 120°C, for example at about 80°C. Conversion reactions are conventional and can be derived from literature information.

Compounds of formula (II), (V), (VII) and (XI) are either known compounds or they 15 can be prepared from known compounds by conventional methods, for example as described in WO 98/43960 and WO 98/13350.

Compounds of formula (III), (IV), (VI) and (VII) are also known compounds (see for example Rev. Chim. (Bucharest) (1988), 39(6), 477-82 and DD 110651: 74.01.05) or they can be prepared from known compounds using conventional methods.

20 Compounds of the invention are useful in the inhibition of MEK enzyme activity and can be used in the treatment of proliferative disease. They will suitably be in the form of a pharmaceutical composition, in combination with a pharmaceutically acceptable carrier. Such compositions form a further aspect of the invention.

The compositions of the invention may be in a form suitable for oral use (for example 25 as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile

aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended 5 for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding 10 agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the 15 gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

20 Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or 25 condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters 30 derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and

hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

5 Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved
10 by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional
15 excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum
20 tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

25 Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using
30 one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable

solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal 5 temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well 10 known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30 μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then 15 conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing 20 finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial 25 Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent 30 compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will

generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

5 The size of the dose for therapeutic or prophylactic purposes of a compound of formula (I), (IA) or (IB) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of formula (I), (IA) or (IB) are useful in treating diseases or medical conditions which are due alone or in part to
10 the effects MEK enzymes.

In using a compound of formula (I), (IB) or (IC) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for
15 intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

According to a further aspect of the invention there is provided a compound of the
20 formula (I), (IA) or (IB) or a pharmaceutically-acceptable salt or prodrug or solvate thereof, as defined hereinbefore, for use in a method of treatment of the human or animal body by therapy.

We have found that the compounds of the present invention possess potent anti-tumour activity which it is believed is obtained by way of inhibition the MAPK pathway and,
25 in particular, inhibition of MEK enzyme

Accordingly the compounds of the present invention are of value as anti-proliferative agents.

Thus according to an aspect of the invention there is provided the use of a compound of formula (I), (IA) or (IB) or a pharmaceutically-acceptable salt, prodrug or solvate thereof,
30 as defined hereinbefore in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I),
5 (IA) or (IB) or a pharmaceutically-acceptable salt thereof, prodrug or solvate thereof as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a compound of formula (I), (IA), (IB) or a pharmaceutically-acceptable salt thereof, prodrug or solvate thereof as defined hereinbefore in the manufacture of a medicament for use in the prevention
10 or treatment of solid tumour disease in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), (IA), (IB) or a pharmaceutically-acceptable
15 salt thereof, prodrug or solvate thereof as defined hereinbefore

According to a further aspect of the invention there is provided the use of a compound of formula (I), (IA), (IB) or a pharmaceutically-acceptable salt thereof, prodrug or solvate thereof as defined hereinbefore
in the manufacture of a medicament for use in the prevention or treatment of those tumours
20 which are sensitive to inhibition of MEK enzymes.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of MEK enzymes which comprises administering to said animal an effective amount of a compound of formula (I), (IA), (IB) or a pharmaceutically-acceptable salt thereof, prodrug or
25 solvate thereof as defined hereinbefore.

The anti-proliferative treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compounds of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

30 (i) anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(ii) other antiproliferative or antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and

5 tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred antimetabolites disclosed in European Patent Application No. 562734 such as (2S)-2-{o-fluoro-p-[N-{2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamido}-4-(tetrazol-5-yl)butyric acid); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin,

10 idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(iii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene,

15 raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride;

20 (iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example the EGFR tyrosine kinase inhibitors N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (ZD1839), N-(3-ethynylphenyl)-

25 6,7-bis(2-methoxyethoxy)quinazolin-4-amine (CP 358774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family; and

(v) antiangiogenic agents such as those which inhibit vascular endothelial growth factor

30 such as the compounds disclosed in International Patent Applications WO 97/22596,

-60-

WO 97/30035, WO 97/32856 and WO 98/13354 and those that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin).

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products 5 employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of formula (I), (IA), (IB) or a pharmaceutically-acceptable salt thereof, prodrug or solvate thereof as defined hereinbefore and an additional anti-tumour agent 10 as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of the present invention are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of MEK enzyme. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new 15 pharmacological agents.

The invention will now be particularly described by way of the following non-limiting example.

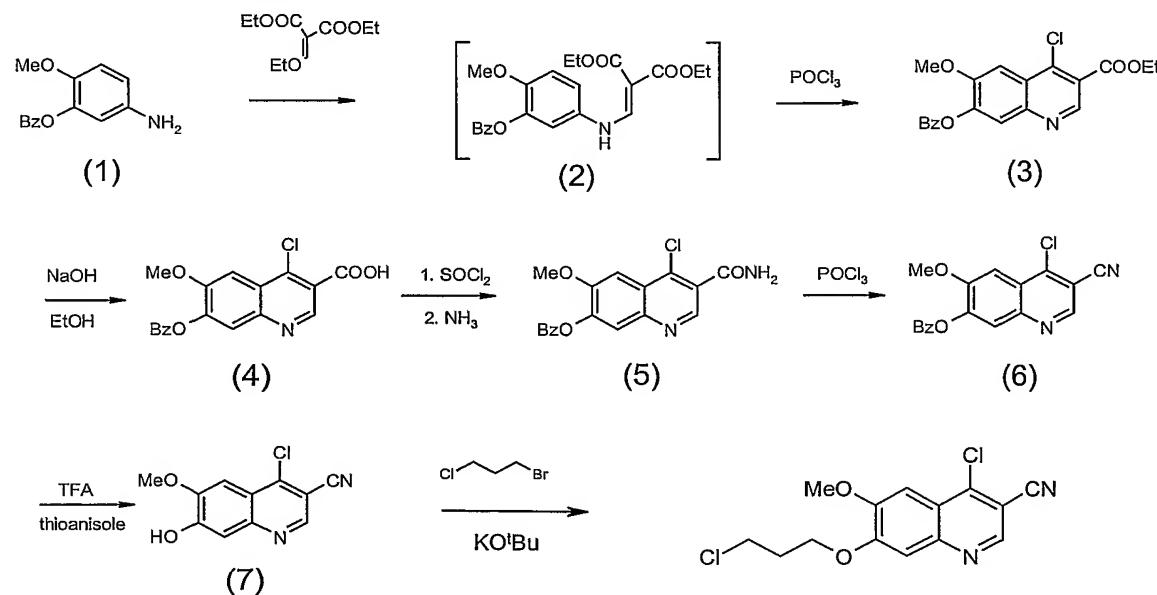
Examples

In the examples the following abbreviations have been used.

5	DMF	-	<u>N,N</u> -dimethylformamide
	THF	-	tetrahydrofuran
	DMSO	-	dimethyl acetamide
	DEAD	-	diethyl azodicarboxylate
	Ph ₃ P	-	triphenylphosphine
10	EDC	-	ethylene dichloride (1,2-dichloroethane)
	DCM	-	dichloromethane (methylenechloride)
	DMAP	-	dimethylaminepyridine
	HOBT	-	N-hydroxybenzotriazole
	EDAC	-	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide
15	KHMDS	-	potassium hexamethyldisilazane (potassium bis(trimethylsilyl)amide)

Preparation of key intermediates

a) Chloroquinoline intermediates – Intermediate A



A mixture of (1) (10.36g., 45.3 mmole) and diethylethoxymethylene malonate (9mL, 45.3 mmole) was heated at 110 °C for 1 hour and then allowed to cool overnight. The mixture was evaporated and the product (2) used in the next step without further purification.

Mass Spectrum m/e 400 ($M^+ + H$).

5 **Preparation of (3)**

A mixture of (2) (assumed 45.3 mmole) and phosphoryl chloride (83.3mL, 906 mmole) was heated at 115 °C for 18 hours. After cooling, the solution was evaporated to remove excess phosphoryl chloride. The residue was treated with ice and aqueous ammonia to hydrolyse the remaining phosphoryl chloride. The solid product was filtered off and dried in a vacuum oven

10 to give a cream coloured solid, 9.0g (53% yield).

Mass Spectrum m/e 372 ($M^+ + H$).

Preparation of (4)

A mixture of (3) (9.0g, 24.2 mmole) was stirred in ethanol (48.3mL) for 15 minutes at ambient temperature to give a smooth suspension. Aqueous sodium hydroxide solution

15 (2.0M, 48.3mL, 96.7 mmole) was added and the mixture stirred for 18 hours at ambient temperature. The ethanol was removed by rotary evaporation and the resulting solution was acidified to pH 2 with hydrochloric acid while stirring. The precipitate was filtered off and dried in a vacuum oven to give an orange solid, 7.19g (86% yield).

Mass Spectrum m/e 344 ($M^+ + H$).

20 **Preparation of (5)**

A mixture of (4) (7.18g, 20.9 mmole) and thionyl chloride (90 mL) was refluxed for 2 hours. After cooling the excess thionyl chloride was removed by rotary evaporation and the residue was suspended in acetone (175mL) and the resulting suspension cooled in an ice-bath.

Aqueous ammonia (S.G. 0.880, 20mL) was added gradually, keeping the temperature below

25 10 °C. The resulting suspension was filtered off, washed with water and air-dried to give a solid, 5.15g (75% yield).

Mass Spectrum m/e 343 ($M^+ + H$).

Preparation of (6)

A mixture of (5) (20.55g, 60 mmole) and phosphoryl chloride (250mL) was heated and stirred

30 at 120 °C for 4 hours when the starting material had dissolved. Heating and stirring was continued at 110 °C for 18 hours. After cooling, the solution was evaporated to remove excess phosphoryl chloride. Last traces of phosphoryl chloride were removed by azeotroping

with toluene. The residue was treated with ice and aqueous ammonia to remove acidity. The solid product was filtered off and dried in a vacuum oven to give a grey solid, 19.23g (99% yield).

(This may also be prepared as described in WO 9843960)

5 Mass Spectrum m/e 325 (M⁺+H).

Preparation of (7)

A mixture of (6) (19.23g, 60.0 mmole) and trifluoroacetic acid (300 ml) and thioanisole (35ml) was refluxed in a nitrogen atmosphere for 3 hours. After cooling the trifluoroacetic acid was removed by rotary evaporation and the oily residue was stirred with ice and water

10 and basified with aqueous ammonia (S.G. 0.880). The resulting suspension was filtered and the solid was washed successively with water, ethyl acetate and diethyl ether and then dried to give a khaki solid, 13.74g (97% yield).

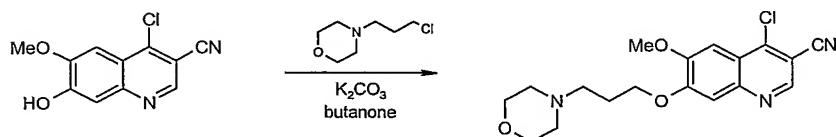
Mass Spectrum m/e 235 (M⁺+H).

Preparation of (8)

15 Potassium tert-butoxide (5.0g) was added portionwise to a stirred solution of (7) (10 g) in DMA (200ml) cooled to 5°C under an atmosphere of nitrogen. The mixture was stirred at ambient temperature for 30min. and then cooled to 5°C. 1-chloro-3-bromopropane (7.4g) was added followed by tetrabutylammonium iodide (1.57g) and 18-crown-6 (0.5g) and the mixture stirred at ambient temperature for 16hr. The DMA was removed in vacuo and the residue 20 partitioned between ethyl acetate and water. The organic extracts were dried and evaporated to dryness. The product was purified by flash column chromatography on silica eluting with 1-2 % methanol in dichloromethane to give (8) as a white solid (6.5g).

Mass Spectrum m/e 311 (M⁺+H).

25 a1) **Preparation of Intermediate A1- (4-chloro-6-methoxy-7-[3-(1-morpholino)propoxy]-3-quinolinecarbonitrile)**



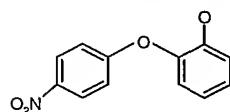
A mixture of 4-chloro-6-methoxy-7-hydroxy-3-quinolinecarbonitrile (2.34g, 10.0 mmole) and

30 1-(3-chloropropyl)morpholine (2.45g, 15.0 mmole) and anhydrous potassium carbonate

(2.07g, 15.0 mmole) suspended in butanone (150mL) was stirred in a oil-bath at 88 °C for 96 hours. The suspension was filtered hot to remove inorganics and the filtrate was allowed to cool and then evaporated to ca. 100mL. A solid precipitated on standing for 72 hours. The solid was filtered off and washed with a little acetone and then dried to give a white solid, 5 0.54g (15% yield).

Mass Spectrum m/e 362 (M⁺+H).

b) Preparation of Intermediate B



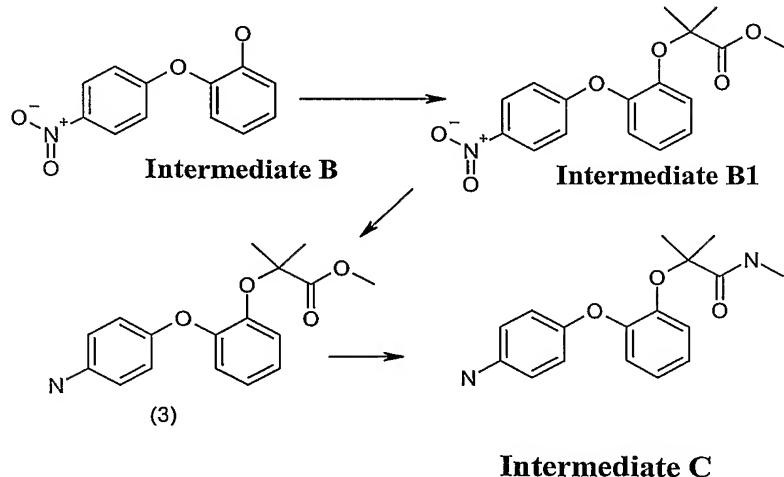
10 Intermediate B

This was prepared by reacting 2-hydroxyphenol (25g) with 4-fluoronitrobenzene (32g) in DMA (250ml) in the presence of potassium tert-butoxide (26.7g) at 140-160°C for 30min. NMR Spectrum (d-6-DMSO, d values) 6.87 (m, 1H), 6.99 (m, 3H), 7.10 (m, 2H), 8.18 (m, 2H), 9.76 (s, 1H)

15

c) Preparation of Intermediate C

The compound was prepared as outlined in the following scheme



Intermediate C

20 Step 1

Intermediate B was reacted with methyl 2-hydroxyisobutyrate in THF at room temperature for 16hr using triphenylphosphine/DEAD as the coupling reagent to give intermediate B1 after chromatography.

Mass Spectrum m/e 332.3 (M+H)⁺

Step 2

Intermediate B1 was reduced to the corresponding aniline by reduction, at room temperature in ethyl acetate solution, with hydrogen and catalytic 5% Pd/C to give intermediate 3.

5 Mass Spectrum m/e 302.38 (M+H)⁺

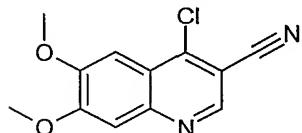
Step 3

Intermediate 3 was converted to the amide by reaction with methylamine in ethanol for 16hr at room temperature. The product was purified by chromatography to give intermediate C.

Mass Spectrum m/e 301.36

10

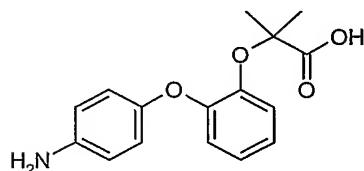
d) **Preparation of Intermediate D**



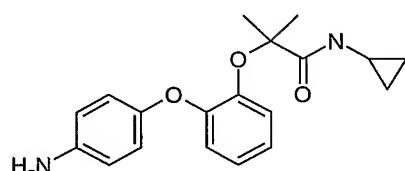
This was prepared as described in WO 9843960, example 34.

15 e) **Preparation of Intermediates E and F**

The compounds were prepared as outlined in the following scheme.



Intermediate E



Intermediate F

Step 1

20 Steps 1 and 2 of the preparation described above to make Intermediate C were followed to prepare intermediate 3.

Step 2

Intermediate 3 was converted to the hydroxide (Intermediate E in the above scheme) by reaction with sodium hydroxide in methanol for 18hr at room temperature

25 Mass Spectrum m/e 288.3 (M⁺H)

Step 3

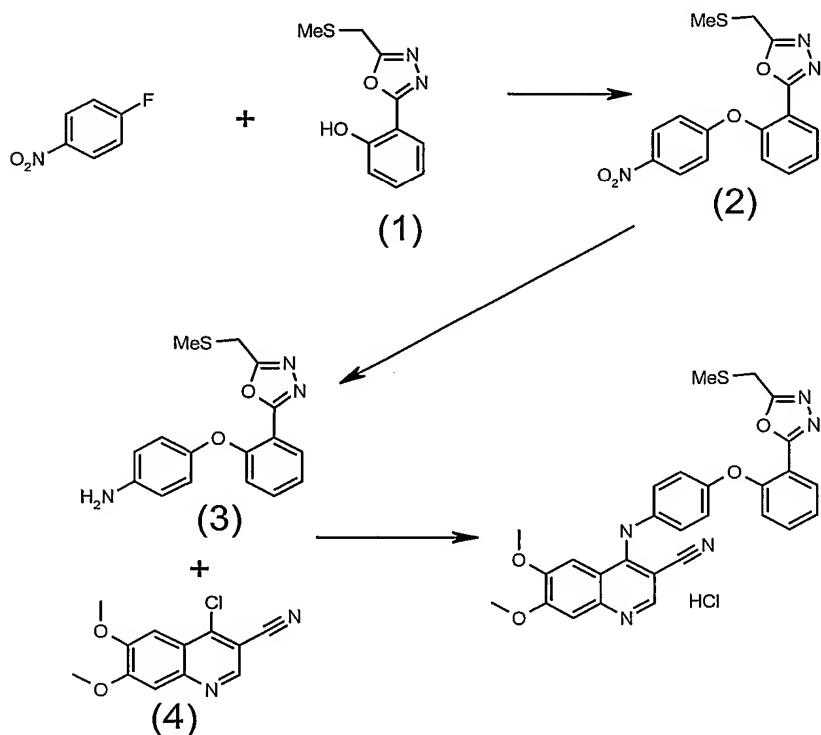
Intermediate E was converted to Intermediate F by reaction with cyclopropylamine in the presence of DMAP/EDC/DCM at room temperature for 18 hrs. The product was purified by chromatography

5 Mass Spectrum m/e 327.3 (M+H)⁺.

Example 1

Preparation of Compound 1 in Table 1

The compound was prepared using the synthesis outlined in the following scheme:



10

Step 1

Intermediate (1) was prepared by heating salicylic hydrazide (1.52g, 10mmol) in $\text{MeSCH}_2\text{C}(\text{OMe})_3$ (15ml) at 100°C for 18hrs.

Mass Spectrum m/e 223 ($M^+ + H$)

15 Step 2

The product of step 1 (1.745g, 7.9mmol) was dissolved in DMA (15ml), -potassium tert-butoxide (953mg, 7.9mmol) was added and the reaction was stirred at ambient temperature for 10minutes. Para-fluoronitrobenzene (1.11g, 7.9mmol) was added and the reaction was heated to 150°C for 90 min. The reaction was cooled and concentrated in vacuo. The residue

was partitioned between ethyl acetate and 2M aqueous sodium hydroxide solution. The aqueous phase was reextracted and the combined organic phase washed with water and brine, dried, filtered and concentrated. The residue was purified by column chromatography using 35 - 40% ethyl acetate in hexane as eluent to yield Intermediate (2).

5 Mass Spectrum m/e 344 ($M^+ + H$)

Step 3

Intermediate 2 (93mg, 0.27mmol) was suspended in 1:1 ethanol:water (3ml), $Na_2S_2O_4$ (418mg, 2.4mmol) was added and the reaction heated at 100°C for 15 min. The reaction was cooled, 2M aqueous sodium hydroxide solution was added and the reaction was stirred for

10 1hr. The aqueous phase was extracted with ethyl acetate (2x) and the combined organic extracts were washed with water and brine, dried, filtered and concentrated to give Intermediate (3).

Mass Spectrum m/e 314 ($M^+ + H$)

Step 4

15 Intermediate (3) from step 3 above (31mg, 0.1mmol) was mixed with 4-chloro-3-cyano-6,7-dimethoxy quinoline (4) (23mg, 0.09mmol), prepared as described WO 9843960, in 1-propanol (3ml) and the mixture was stirred and heated at 110°C for 18 hours. The mixture was cooled to ambient temperature and then filtered. The crystals were washed with a small volume of 1-propanol and then dried to give compound 1.

20 Mass Spectrum m/e 526 ($M^+ + H$)

NMR Spectrum (d-6-DMSO, d values) 2.10, (s, 3H), 4.00 (s, 3H), 4.00 (s, 3H), 4.00 (s, 2H), 7.15 (m, 3H), 7.35 (t, 1H), 7.45 (d, 2H), 7.45 (s, 1H), 7.60 (t, 1H), 8.00 (d, 1H), 8.20 (s, 1H), 8.90 (s, 1H), 11.20 (br s, 1H).

25 **Example 2**

Preparation of Compound 2 in Table 1

Compound No 1 (56mg, 0.1mmol) prepared as described in Example 1 was suspended in acetic acid (2.7ml). Peracetic acid (39% in acetic acid, 0.05ml, 0.29mmol) was added dropwise and the reaction was stirred overnight. A further portion of peracetic acid (0.05ml)

30 was added and the reaction stirred overnight again. The reaction was concentrated in vacuo and the residue suspended in dichloromethane. Potassium carbonate was added and the mixture stirred for 30min at ambient temperature. The reaction was filtered and concentrated

to a residue which was purified by Bond Elut chromatography eluting with DCM increasing to 1.5% methanol in DCM to give Compound No. 2.

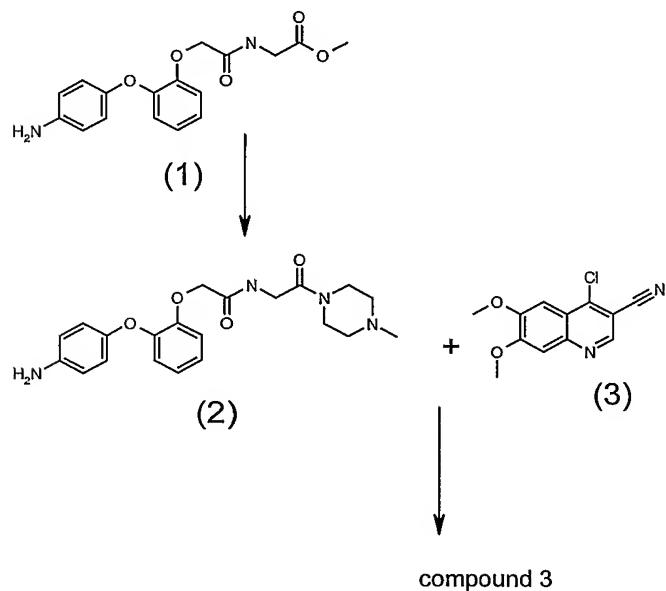
Mass Spectrum m/e 558 ($M^+ + H$)

NMR Spectrum ($CDCl_3$, δ values) 3.10, (s, 3H), 3.80 (s, 3H), 4.00 (s, 3H), 4.60 (s, 2H), 7.00
5 (d, 2H), 7.10 (d, 1H), 7.10 (s, 1H), 7.10 (br s, 1H), 7.15 (d, 2H), 7.25 (s, 1H), 7.30 (t, 1H),
7.55 (t, 1H), 8.10 (dd, 1H), 8.55 (s, 1H)

Example 3

Preparation of Compound No. 3 in Table 1

10 The compound was prepared as outlined in the following scheme:



Step 1

4-nitro-fluorobenzene and 2-(carboxymethoxy)phenol were reacted together in DMA in the presence of potassium butoxide for 2 hours at 150°C to yield 4-(2-carboxymethoxy)-

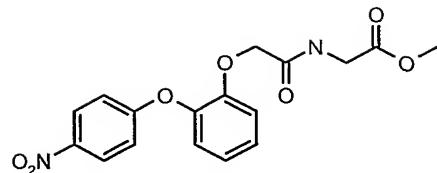
15 phenoxy)nitrobenzene.

Mass Spectrum m/e 288 ($M - H^+$)

Step 2

A solution of the product of step 1 in DMA was then coupled with methyl glycine using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDAC), dimethylaminopyridine (DMAP) and N-

20 hydroxybenzotriazole (HOBT) to yield the intermediate of formula



Mass Spectrum m/e 361.17 ($M^+ + H$).

Step 3

Reduction of the product of step 2 to the corresponding amine (Intermediate 1), was effected
5 by hydrogenation in the presence of a 5% Pd/C catalyst.

Mass Spectrum m/e 331.14($M^+ + H$).

Step 4

Intermediate (1) (300mg) was reacted with N-methylpiperazine (1ml) in methanol (10ml) for
3 days at reflux. The product was purified by flash column chromatography to yield
10 Intermediate 2 above (240mg) as a gum.

Mass Spectrum m/e 399.36 ($M^+ + H$).

Step 5

Intermediate (2) from step 4 above (230mg) was mixed with 4-chloro-3-cyano-6,7-dimethoxy
quinoline (Intermediate 3) (143mg), prepared as described WO 9843960, in 1-propanol
15 (15ml) and a solution of 1M hydrogen chloride in ether (0.6ml) was added. The mixture was
stirred and heated at 100°C for 2 hours. The mixture was cooled to ambient temperature and
then filtered. The crystals were washed with a small volume of 1-propanol and then dried to
give the final product, Compound No. 3 (332mg) as a yellow solid.

Mass Spectrum m/e 611.31 ($M^+ + H$).

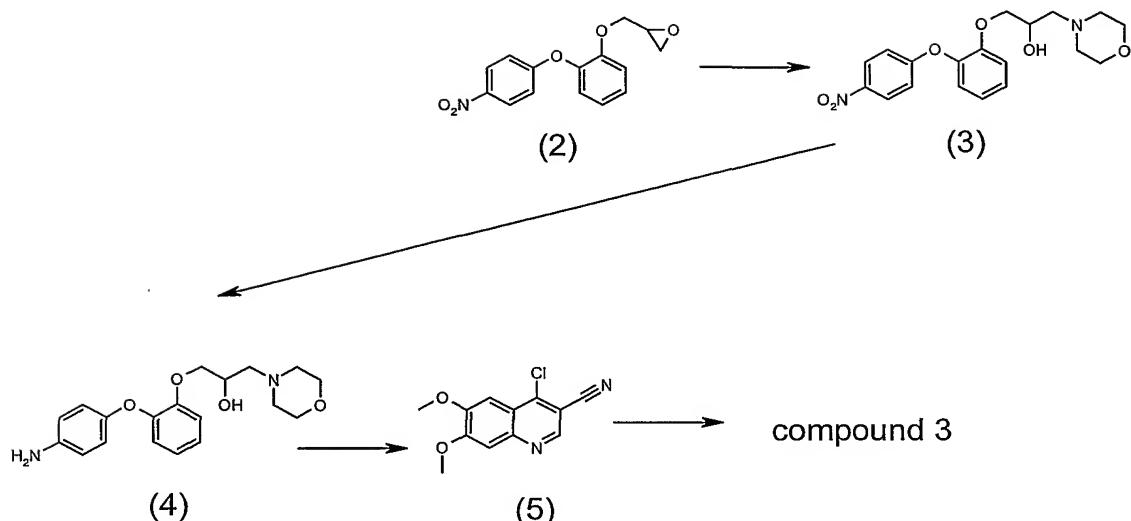
20 NMR Spectrum (d-6-DMSO, δ values) 2.72 (s, 3H), 2.80-3.60 (m, 6H), 3.92-4.23 (m, 3H),
3.98 (d, 6H), 4.27-4.48 (m, 1H), 4.57(s, 2H), 6.94-7.1 (m, 4H), 7.14 (d, 2H), 7.40 (d, 2H),
7.48 (s, 1H), 7.85 (t, 1H), 8.21 (s, 1H), 8.89 (s, 1H), 11.02-11.18(br.s, 1H), 11.18-11.26 (br.s,
1H).

Example 4

25 **Preparation of Compound No 4**

The compound was prepared as outlined in the following scheme:

-70-



Step 1

Intermediate B, described above (1g) was reacted with epichlorohydrin (0.41g) in tetrahydrofuran (50ml) in the presence of potassium tert-butoxide (7.4ml of 1M solution in 5 THF) and 18-crown-6 ether for 2hr at room temperature and 16hr at reflux to produce intermediate 2 (0.95g) in the above scheme.

Step 2

The product of step 1 was reacted with morpholine in n-propanol to produce intermediate 3. Mass Spectrum m/e 375.29 ($M^+ + H$).

10 Step 3

The product of step 2 was reduced with hydrogen and 5% Pd/C to produce intermediate 4.

Mass Spectrum m/e 345.41 ($M^+ + H$).

Step 4

Intermediate D was reacted intermediate 4 in n-propanol solution at 100°C for 2hr to give the title product.

Mass Spectrum m/e 557.40 ($M^+ + H$).

NMR Spectrum (d-6-DMSO, δ values) 2.93-3.66 (m, 6H), 3.7-3.95 (m, 6H), 3.98 (s, 3H), 4.01(s, 3H), 4.26 (m, 1H), 6.95-7.07 (m, 3H), 7.1 (d, 1H), 7.2 (m, 2H), 7.4 (d, 2H), 7.49 (s, 1H), 8.32 (s, 1H), 8.89(s, 1H).

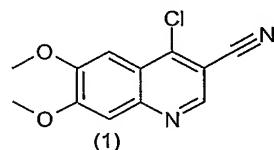
Example 5**Preparation of Compound No. 5 in Table 1**

The title compound was prepared by a method analogous to that described in Example 4 but using piperidine instead of morpholine in step 3.

5 Mass Spectrum m/e 555.33 ($M^+ + H$).

NMR Spectrum (d-6-DMSO, δ values) 1.27-1.48 (m, 1H), 1.56-1.91 (m, 5H), 2.8-3.05 (m, 4H), 3.25-3.39 (m, 2H), 3.82-3.97 (m, 2H), 3.98 (s, 3H), 4.00 (s, 3H), 4.2 (m, 1H), 6.93-7.08 (m, 3H), 7.11 (d, 1H), 7.2 (m, 2H), 7.40 (d, 2H), 7.50 (s, 1H), 8.37 (s, 1H), 8.89 (s, 1H), 9.71 (br.s, 1H), 11.36-11.44 (br.s, 1H).

10

Example 6**Preparation of Compound No. 6 in Table 1**

Intermediate C was reacted with (1) (prepared as described in WO 9843960) in n-propanol

15 solution at 105°C for 3hr to give compound 6.

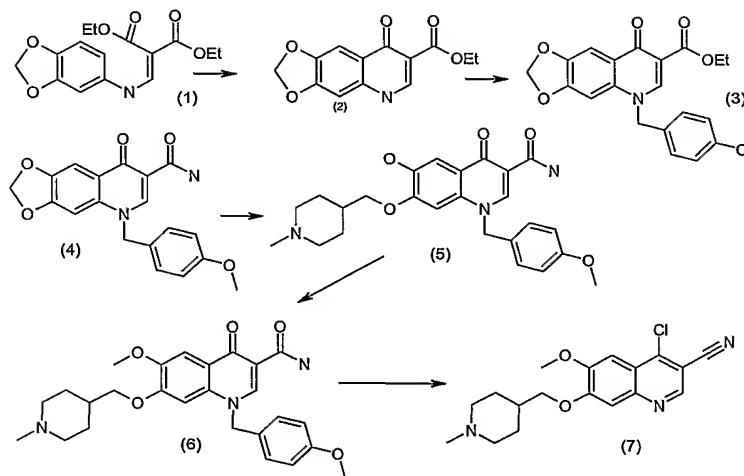
Mass Spectrum m/e 513.32 ($M+H$)⁺

NMR Spectrum (d-6-DMSO, δ values) 1.33 (s, 6H), 2.61 (d, 3H), 3.99 (s, 6H), 6.99 (d, 3H), 7.04 - 7.18 (m, 3H), 7.43 (d, 2H), 7.48 (s, 1H), 7.76 (m, 1H), 8.18 (s, 1H), 8.92 (s, 1H), 11.16 (bs, 1H).

20

Example 7**Preparation of Compound No. 7 in Table 1**

The compound was prepared as outlined in the following scheme



Step 1

Intermediate (1) was prepared by reacting together methylenedioxylaniline (51g, 0.37mol) and diethylethoxymethylenemalonate (75.1ml, 0.37mol) in ethanol at 80°C for 1hour.

5 NMR Spectrum (d-6-DMSO, δ values) 1.30(t, 3H), 1.37 (t, 3H), 4.22 (q, 2H), 4.29 (q, 2H), 6.99 (s, 2H), 6.56 (m, 1H), 6.66 (d, 1H), 6.79 (d, 1H), 8.37 (d, 1H), 10.94 (bd, 1H).

Step 2

The product of step 1 was converted to Intermediate (2) above by contact with Dowtherm A for 1 hour at 250-260°C.

10 NMR Spectrum (d-6-DMSO, d values) 1.24 (t, 3H), 4.17 (q, 2H), 6.13 (s, 2H), 7.03 (s, 1H), 7.43 (s, 1H), 8.49 (s, 1H).

Step 3

Reaction of the product of step (2) (20.3g,) with 4-methoxybenzylchloride (11.9ml, 81.6mmol) in DMA (200ml) in the presence of potassium carbonate for 3 hours at 100°C

15 yielded Intermediate 3

Mass Spectrum m/e 382 ($M+H$)⁺.

Step 4

The product of step 3 mixed with formamide (91.8mmol, 3.5equiv.) in DMA was heated at 60°C. Sodium methoxide (25% in methanol, 3.9ml, 0.65 equiv.) was added and heating of the 20 mixture continued for 90mins to yield Intermediate 4 in the above scheme.

Mass Spectrum m/e 353 ($M+H$)⁺.

Step 5

The product of step 4 was mixed with N-methyl-4-hydroxymethylpiperidine, potassium (tert)-butoxide and DMA and the mixture heated at 120°C for 20mins. Intermediate (5) was obtained after chromatography.

5 Mass Spectrum m/e 452 (M+H)⁺.

Step 6

Intermediate (5) was mixed with methanol and PPh₃ in DCM and DEAD added, and the mixture allowed to react at room temperature for 18hr to give intermediate 6.

Mass Spectrum m/e 466 (M+H)⁺.

10 **Step 7**

The product of step 6 was then reacted with POCl₃ in MeCN for 18 hours at 110°C to yield Intermediate 7 in the above scheme.

Mass Spectrum m/e 346, 348 (M+H)⁺.

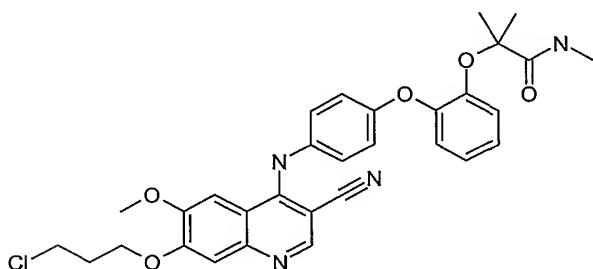
Step 8

15 Intermediate 7 was reacted with intermediate C (prepared as described above) in n-propanol solution at 100°C for 3hr to give, after chromatographic purification, compound 7.

Mass Spectrum m/e 610 (M+H)⁺.

NMR Spectrum (d-6-DMSO + d-4-AcOH, δ values) 1.33 (s, 6H), 1.66 (m, 2H), 1.97 (m, 3H), 2.60 (s, 3H), 2.71 (s, 3H), 2.98 (m, 2H), 3.42 (m, 2H), 3.98 (s, 3H), 4.06 (2H, m), 6.97 (m,

20 4H), 7.09 (m, 3H), 7.41 (d, 2H), 7.55 (s, 1H), 8.24 (m, 1H), 8.87(s, 1H).

Example 8**Preparation of Compound No. 8 in Table 1**

25

(1)

Step 1

Intermediates A and C prepared as described above were reacted in n-propanol solution at 105°C for 3hr to give intermediate 1.

Mass Spectrum m/e 575.25 (M+H)⁺

Step 2

Intermediate 1 was reacted with morpholine at room temperature for 72hr in the presence of sodium iodide to give, after chromatographic purification, compound 8.

5 Mass Spectrum m/e 626.37 (M+H)⁺

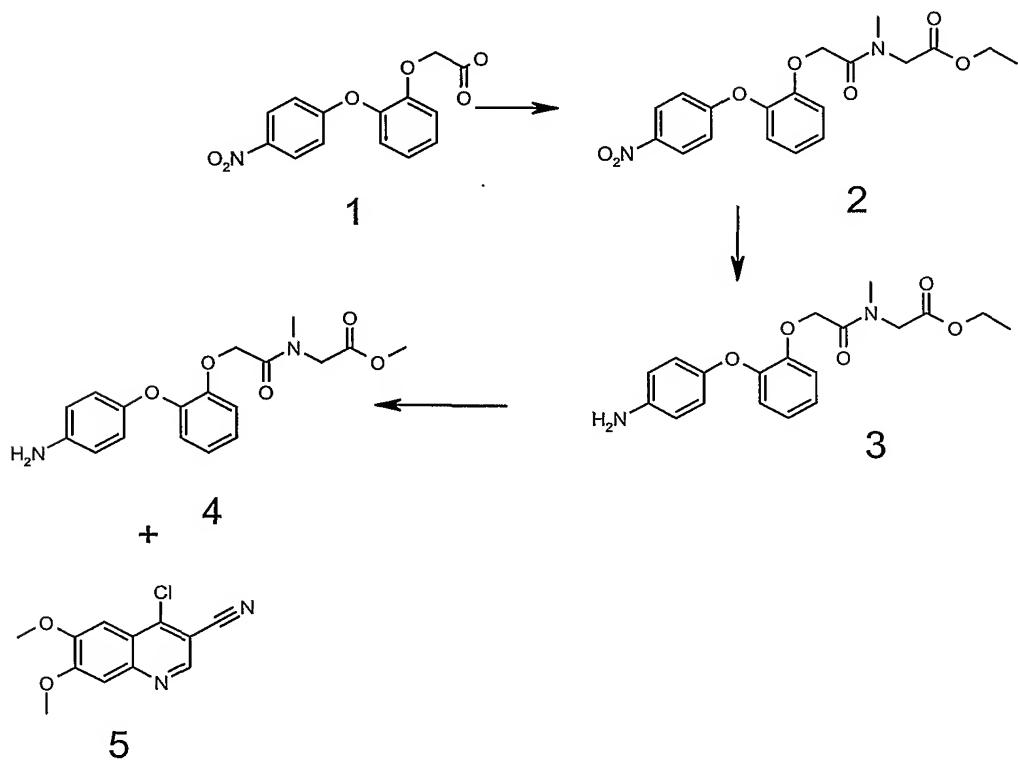
NMR Spectrum (d-6-DMSO D4 Acetic, δ values) 1.34 (s, 6H), 2.32 (m, 2H), 2.60 (s, 3H), 3.04m - 3.17 (m, 2H), 3.29 (t, 2H), 3.41 - 3.55 (m, 2H), 3.73 - 3.86 (m, 2H), 3.90 - 4.01 (m, 5H), 4.30 (t, 2H), 6.98 (d, 3H), 7.05 - 7.19 (m, 3H), 7.42 (d, 2H), 7.49 (s, 1H), 8.14 (s, 1H), 8.91 (s, 1H).

10

Example 9

Preparation of Compound 9 in Table 1

This was prepared as outlined in the following reaction scheme.



15 **Step 1**

4-nitro-fluorobenzene and 2-(carboxymethoxy)phenol were reacted together in DMA in the presence of potassium butoxide for 2hours at 150°C to yield 4-(2-carboxymethoxy)phenoxy)nitrobenzene, intermediate 1.

Mass Spectrum m/e 288 (M-H)⁻

Step 2

A solution of the product of step 1 in DMA was then coupled with ethyl N-methylglycine using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDAC), dimethylaminopyridine (DMAP) and N-hydroxybenzotriazole (HOBT) to yield intermediate 2.

5 **Step 3**

Reduction of the product of step 2 to the corresponding aniline, intermediate 3, was effected by hydrogenation in the presence of a 5% Pd/C catalyst.

Mass Spectrum m/e 359.38 ($M^+ + H$).

10

Step 4

A methanolic solution of intermediate 3 was refluxed for several hours resulting in the production of intermediate 4.

Mass Spectrum m/e 345.32 ($M^+ + H$).

15 **Step 5**

Intermediate 5 (prepared as described in WO 9843960) was reacted intermediate 4 in n-propanol solution at 100°C for 2hr to give the title product.

Mass Spectrum m/e 557.27 ($M^+ + H$).

NMR Spectrum (d-6-DMSO, δ values) 2.82&3.01 (2s, 3H), 3.62&3.68 (2s, 3H), 3.97 (2s, 2H), 4.08&4.27(2s, 2H), 4.76&4.90 (2s, 2H), 6.89-7.06 (m, 5H), 7.06-7.20 (m, 1H), 7.4 (d, 2H), 7.41 (s, 1H), 8.08 (s, 1H), 8.9(s, 1H), 10.90-11.00(br.s, 1H).

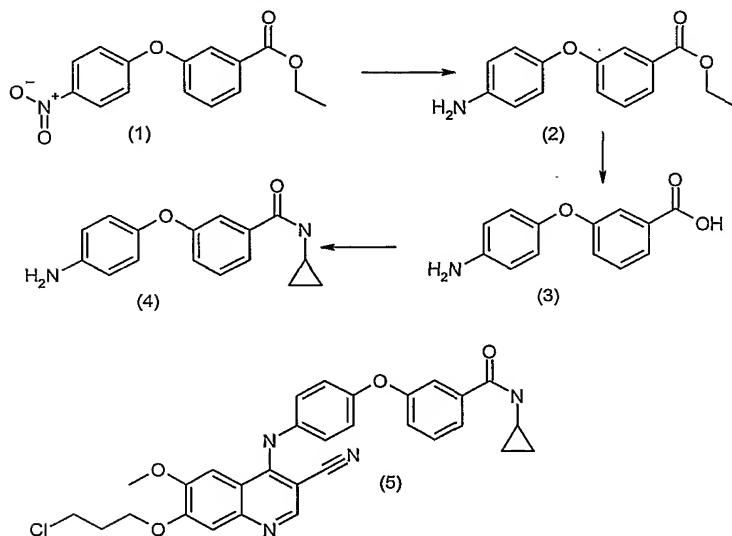
25

30

35

Example 10**Preparation of Compound 10 in Table 1**

The compound was prepared as outlined in the reaction scheme below



5

Step 1

4-fluoro-nitrobenzene and ethyl 3-hydroxybenzoate were reacted together in DMA in the presence of potassium butoxide for 2hours at 150°C to yield intermediate 1.

Mass Spectrum m/e 283.27 (M-H)⁺

10

Step 2

Intermediate 1 was reduced to the corresponding aniline by reduction, at room temperature in ethyl acetate solution, with hydrogen and catalytic 5% Pd/C to give intermediate 2.

15 Mass Spectrum m/e 258.22 (M+H)⁺

Step 3

Intermediate 2 was converted to the carboxylic acid by hydrolysis with 2M aqueous sodium hydroxide solution in ethanol for 16hr at room temperature to give intermediate 3.

Mass Spectrum m/e 230.12 (M+H)⁺

20 **Step 4**

Intermediate 3 was converted to the amide by condensation with cyclopropylamine using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDAC) and dimethylaminopyridine (DMAP) in dichloromethane solution to yield, after chromatographic purification, intermediate 4.

Mass Spectrum m/e 269.27 (M+H)⁺

Step 5

Intermediate 4 was reacted with intermediate A (prepared as described above) in n-propanol solution at 105°C for 3hr to give intermediate 5.

5 Mass Spectrum m/e 543.38 (M+H)⁺

Step 6

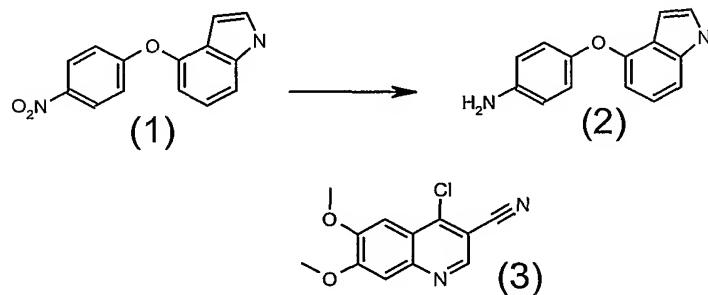
Intermediate 5 was reacted with morpholine in the manner described for Example 8 Step 2 to yield, after chromatographic purification, compound 10.

Mass Spectrum m/e 594.30 (M+H)⁺

10 NMR Spectrum (d-6-DMSO D4 Acetic, δ values) 0.73 - 0.80 (m, 2H), 0.82 - 0.90 (m, 2H), 2.27 - 2.37 (m, 2H), 2.76 - 2.85 (m, 1H), 3.03 - 3.17 (m, 2H), 3.29 (t, 2H), 3.41 - 3.54 (m, 2H), 3.72 - 3.87 (m, 2H), 3.93 - 4.01 (m, 5H), 4.30 (t, 2H), 7.13 - 7.19 (m, 3H), 7.42 (d, 1H), 7.45 - 7.51 (m, 4H), 7.59 (d, 1H), 8.16 (s, 1H), 8.91 (s, 1H).

15 **Example 11**

Preparation of Compound No 11 in Table 2



Step 1

4-Fluoro-nitrobenzene and 4-hydroxyindole were reacted together in DMA in the presence of 20 potassium tert-butoxide in the manner described for Example 7 step 1 to give, after chromatographic purification, intermediate 1.

Mass Spectrum m/e 255 (M⁺+H)

Step 2

Intermediate 1 was reduced to the corresponding aniline by reduction, at room temperature in 25 ethyl acetate solution, with hydrogen and catalytic 5% Pd/C to give intermediate 2.

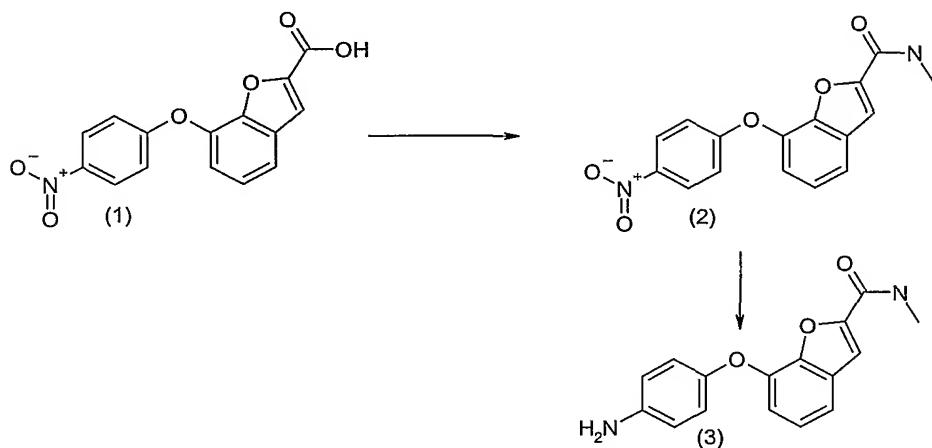
Mass Spectrum m/e 225 (M⁺+H)

Step 3

Intermediate 2 was reacted with intermediate 3 (as described in WO 9843960) in n-propanol solution at 110°C for 18hr to give compound 11.

Mass Spectrum m/e 437 (M^++H)

5 NMR Spectrum (d-6-DMSO, δ values) 4.00 (s, 6H), 6.20 (t, 1H), 6.60 (d, 1H), 7.00 (d, 1H), 7.05 (d, 2H), 7.25 (m, 2H), 7.40 (d, 2H), 7.50 (s, 1H), 8.20 (s, 1H), 8.90 (s, 1H), 11.20 (br s, 1H), 11.30 (br s, 1H).

Example 12**10 Preparation of Compound No 12 in Table 3****Step 1**

4-Fluoro-nitrobenzene was reacted with 2-carboxy-7-hydroxy-benzofuran in DMA in the presence of potassium butoxide at 120°C for 2 hrs to give intermediate 1.

Mass Spectrum m/e 254.1 ($M-CO_2H$)⁺.

Step 2

Intermediate 1 was then reacted with methylamine in the presence of DMAP/HCl/EDC/DCM at room temperature for 18 hrs to give intermediate 2.

20 Mass Spectrum m/e Mass ion not observed (M^++H)⁺.

NMR Spectrum (d-6-DMSO, δ values) 2.74 (d, 3H), 7.17 (d, 2H), 7.27 (d, 1H), 7.37 (t, 1H), 7.59 (s, 1H), 7.69 (d, 1H), 8.22 (d, 2H), 8.54 (d, 1H).

Step 3

Intermediate 2 was reduced to the corresponding aniline by reduction at room temperature in 25 ethyl acetate solution, with hydrogen and catalytic 5% Pd/C for 4 hrs to give intermediate 3.

Mass Spectrum m/e 283.4 (M+H)⁺.

Step 4

Intermediate 3 was reacted with Intermediate D, prepared as described above, in n-propanol solution at 105°C for 3hrs to give compound 12.

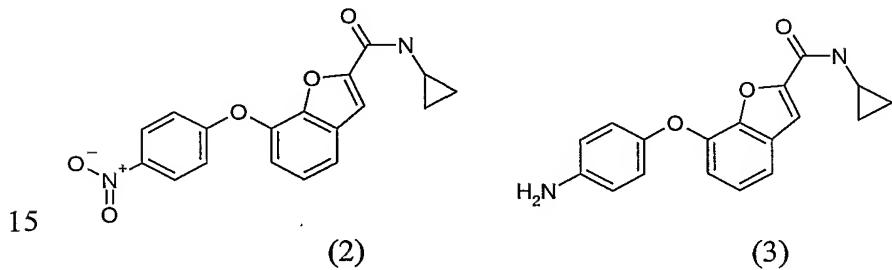
5 Mass Spectrum m/e 495.5 (M+H)⁺.

NMR Spectrum (d-6-DMSO, δ values) 2.89 (d, 3H), 3.99 (s, 6H), 6.99 (d, 1H), 7.21 – 7.30 (m, 3H), 7.45 – 7.55 (m, 4H), 7.58 (s, 1H), 8.16 (s, 1H), 8.47 (d, 1H), 8.94 (s, 1H).

Example 13

10 **Preparation of Compound No 13 in Table 3**

This was prepared by a similar route to that described for example 12 starting with intermediate 1 of example 12.



Step 1

Intermediate 1 was reacted with methylamine in the presence of DMAP/ HCl/EDC/DCM at

20 room temperature for 18 hrs to give intermediate 2.

Mass Spectrum m/e Mass ion not observed (M+H)⁺.

NMR Spectrum (d-6-DMSO, δ values) 0.58 (m, 2H), 0.68 (m, 2H), 2.79 (m, 1H), 7.19 (m, 2H), 7.26 (d, 1H), 7.38 (t, 1H), 7.61 (s, 1H), 7.69 (d, 1H), 8.25 (m, 2H), 8.66 (d, 1H) .

Step 2

25 Intermediate 2 was reduced to the corresponding aniline by reduction at room temperature in ethyl acetate solution, with hydrogen and catalytic 5% Pd/C for 4 hrs to give intermediate 3.

Mass Spectrum m/e 309.4 (M+H)⁺.

Step 4

Intermediate 3 was reacted with Intermediate D, prepared as described above in n-propanol

30 solution at 105°C for 3hrs to give compound 13.

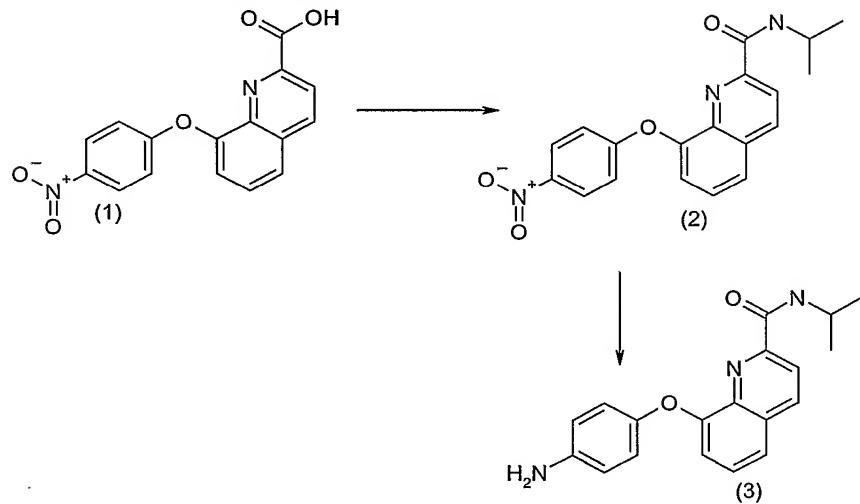
Mass Spectrum m/e 521.5 (M+H)⁺.

NMR Spectrum (d-6-DMSO, δ values) 0.64 (m, 2H), 0.70 (m, 2H), 2.85 (m, 1H), 4.00 (s, 6H), 6.95 (d, 1H), 7.00 – 7.09 (m, 3H), 7.48 – 7.55 (m, 4H), 7.60 (s, 1H), 8.16 (s, 1H), 8.64 (d, 1H), 8.92 (s, 1H).

5

Example 14

Preparation of Compound No 14 in Table 4



10 Step 1

4-Fluoro-nitrobenzene was reacted with 2-carboxy-8-hydroxy-quinoline in DMA in the presence of potassium tert-butoxide at 120°C for 2 hrs to give intermediate 1.

Mass Spectrum m/e 311.2 (M+H)⁺.

Step 2

15 Intermediate 1 was converted to intermediate 2 by reaction with isopropylamine in the presence of DMAP/EDC/DCM for 18hrs at room temperature.

Mass Spectrum m/e 352.3 (M+H)⁺.

Step 3

Intermediate 2 was reduced to the corresponding aniline by reduction at room temperature in

20 ethyl acetate solution, with hydrogen and catalytic 5% Pd/C for 18 hrs.

Mass Spectrum m/e 322.4 (M+H)⁺.

Step 4

Intermediate 3 was reacted with Intermediate D, prepared as described above, in n-propanol solution at 105°C for 3hrs to give compound 14.

Mass Spectrum m/e 534.4 (M+H)⁺.

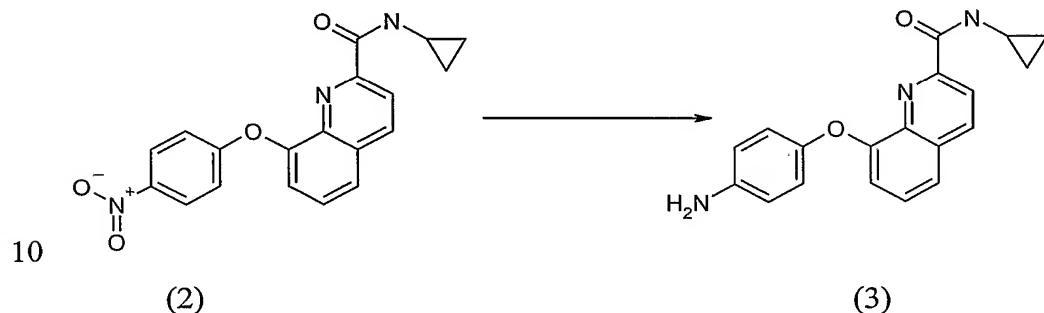
NMR Spectrum (d-6-DMSO, δ values) 1.19 (d, 6H), 4.04 (m, 1H), 7.20 (d, 2H), 7.43 – 7.50 (m, 3H), 7.53 (d, 1H), 7.69 (t, 1H), 7.85 (d, 1H), 7.91 (d, 1H), 8.10 – 8.17 (m, 2H), 8.60 (d, 1H), 8.91 (s, 1H).

5

Example 15

Preparation of Compound No 15 in Table 4

This was prepared by a similar route to that described for example 14 starting with intermediate 1 of example 14.



Step 1

Intermediate 1 was converted to intermediate 2 by reaction with cyclopropylamine in the presence of DMAP/EDC/DCM for 18hrs at room temperature.

15 Mass Spectrum m/e 350.3 (M+H)⁺.

Step 2

Intermediate 2 was reduced to the corresponding aniline by reduction at room temperature in ethyl acetate solution, with hydrogen and catalytic 5% Pd/C for 3 hrs.

Mass Spectrum m/e 320.3 (M+H)⁺.

20 Step 3

Intermediate 3 was reacted with Intermediate D, prepared as described above, in n-propanol solution at 105°C for 3hrs

Mass Spectrum m/e 532.3 (M+H)⁺.

NMR Spectrum (d-6-DMSO, δ values) 0.62 (m, 2H), 0.74 (m, 2H), 2.86 (m, 1H), 3.97 (s, 25 6H), 7.19 (d, 2H), 7.41 – 7.50 (m, 4H), 7.66 (t, 1H), 7.87 (d, 1H), 8.06 (d, 1H), 8.11 – 8.16 (m, 2H), 8.60 (d, 1H), 8.90 (s, 1H).

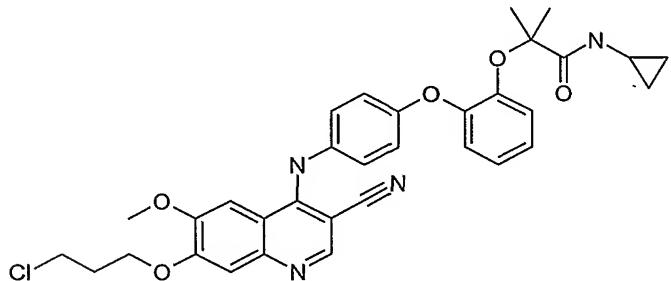
Example 15 A**Preparation of Compound No 15 A in Table 5**

This was prepared by reacting Intermediates D and F, described above, in n-propanol solution
5 at 105°C for 3hrs.

Mass Spectrum m/e 539.3 (M+H)⁺.

NMR Spectrum (d-6-DMSO, δ values) 0.47 (m, 2H), 0.62 (m, 2H), 1.38 (s, 6H), 2.70 (m, 1H), 4.02 (s, 6H), 6.95 – 7.22 (m, 6H), 7.47 (s, 1H), 7.50 (s, 2H), 7.94 (d, 1H), 8.17 (s, 1H), 8.94 (s, 1H), 11.07 (bs, 1H).

10

Example 16**Preparation of Compound No 16 in Table 5**

(1)

15

Step 1

This was prepared by reacting Intermediate A with Intermediate F in n-propanol solution at 105°C for 3.5hr to form Intermediate 1

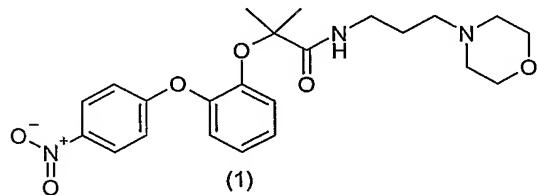
Mass Spectrum m/e 601.3 (M+H)⁺

20 **Step 2**

Intermediate 1 was then reacted with morpholine in sodium iodide at room temperature for 5 days. The product was purified by chromatography.

Mass Spectrum m/e 652.6 (M+H)⁺

NMR Spectrum (d-6-DMSO d-4-Acetic, δ values) 0.46 (m, 2H), 0.61 (m, 2H), 1.36 (s, 6H),
25 2.36 (m, 2H), 2.71 (m, 1H), 3.15 (m, 2H), 3.33 (m, 2H), 3.52 (m, 2H), 3.84 (m, 2H), 3.93 – 4.05 (m, 5H), 4.34 (t, 2H), 6.97 – 7.22 (m, 6H), 7.47 (d, 2H), 7.53 (s, 1H), 7.91 (d, 1H), 8.19 (s, 1H), 8.94 (s, 1H).

Example 17**Preparation of Compound No 17 in Table 5****5 Step 1**

Intermediate (2), example 43 was reacted with 3-(morpholino)propylamine in the presence of DMAP/EDC/DCM for 18 hrs at room temperature to produce Intermediate 1. The product was purified by chromatography.

Mass Spectrum m/e 444.4 (M+H)⁺.

10 Step 2

Intermediate 1 was then converted to the corresponding aniline by reduction at room temperature in ethyl acetate solution with hydrogen and catalytic 5% Pd/C.

Mass Spectrum m/e 414.4 (M+H)⁺.

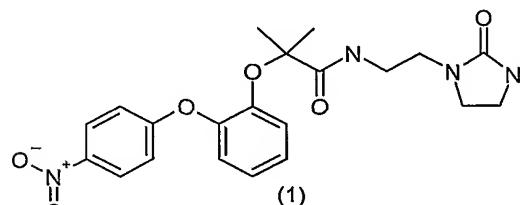
Step 3

15 The aniline derivative was then reacted with Intermediate D in n-propanol solution in the presence of 1.0M Ethereal HCl at a temperature of 105°C for 3 hrs.

Mass Spectrum m/e 626.3 (M+H)⁺.

NMR Spectrum (d-6-DMSO d-4-Acetic, δ values) 1.34 (s, 6H), 1.85 (m, 2H), 2.98 (m, 4H), 3.16 (m, 2H), 3.31 (m, 2H), 3.76 (m, 2H), 3.88 – 3.97 (m, 2H), 3.99 (s, 3H), 4.00 (s, 3H), 6.96

20 – 7.02 (m, 3H), 7.04 – 7.20 (m, 3H), 7.40 – 7.48 (m, 3H), 8.04 (t, 1H), 8.18 (s, 1H), 8.92 (s, 1H).

Example 18**Preparation of Compound No 18 in Table 5**

Step 1

This was prepared by an analogous route to that described for example 17 except that 3-(morpholino)propylamine was replaced by 2-(2-oxoimidazolidin-1-yl)ethylamine to produce Intermediate 1, shown above. The product was purified by chromatography.

Mass Spectrum m/e 429.4 (M+H)⁺.

Step 2

The aniline corresponding to intermediate 1 was prepared as described in example 17.

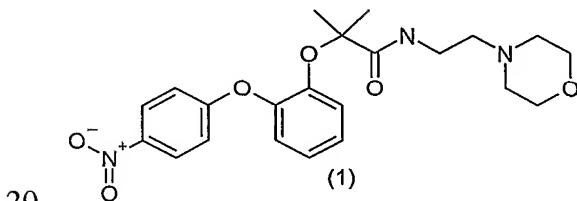
Mass Spectrum m/e 399.4 (M+H)⁺.

10 Step 3

The aniline derivative was converted to compound 18 by reaction with Intermediate D as described in example 17.

Mass Spectrum m/e 611.5 (M+H)⁺.

NMR Spectrum (d-6-DMSO d-4-Acetic, δ values) 1.31 (s, 6H), 3.07 – 3.23 (m, 6H), 3.26 – 15 3.34 (m, 2H), 3.96 (s, 3H), 3.98 (s, 3H), 6.97 – 7.18 (m, 6H), 7.40 (d, 2H), 7.45 (s, 1H), 7.84 (t, 1H), 8.08 (s, 1H), 8.94 (s, 1H).

Example 19**Preparation of Compound No 19 in Table 5****Step 1**

This was prepared by an analogous route to that described for example 18 except that 3-(morpholino)propylamine was replaced by 3-(morpholino)ethylamine to produce Intermediate 1, shown above. The product was purified by chromatography.

25 Mass Spectrum m/e 430.4 (M+H)⁺.

Step 2

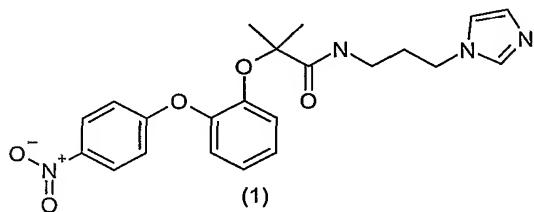
The aniline derivative corresponding to intermediate 1 was prepared as described in example 17. Mass Spectrum m/e 400.4 (M+H)⁺.

Step 3

The aniline derivative of step 2 was converted to compound 19 by reaction with Intermediate D as described in example 17.

Mass Spectrum m/e 612.4 (M+H)⁺.

5 NMR Spectrum (d-6-DMSO δ-4-Acetic, δ values) 1.36 (s, 6H), 3.07 (m, 2H), 3.15 (m, 2H), 3.39 (m, 2H), 3.51 (m, 2H), 3.74 (m, 2H), 3.90 (m, 2H), 3.99 (s, 6H), 6.96 – 7.03 (m, 3H), 7.09 – 7.19 (m, 3H), 7.42 (s, 2H), 7.46 (s, 1H), 8.16 (s, 1H), 8.20 (t, 1H), 8.92 (s, 1H).

Example 20**10 Preparation of Compound No 20 in Table 5****Step 1**

This was prepared by an analogous route to that described for example 18 except that 3-

15 (morpholino)propylamine was replaced by 3-(imidazol-1-yl)propylamine to produce Intermediate 1, shown above. The product was purified by chromatography.

Mass Spectrum m/e 425.4 (M+H)⁺.

Step 2

The aniline derivative corresponding to intermediate 1 was prepared as described in example

20 17. Mass Spectrum m/e 395.4 (M+H)⁺.

Step 3

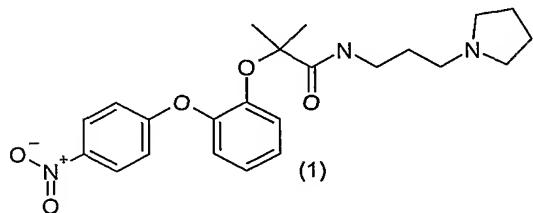
The aniline derivative of step 2 was converted to compound 20 by reaction with Intermediate D as described in example 17. The product was purified by chromatography: yes

Mass Spectrum m/e 607.5 (M+H)⁺.

25 NMR Spectrum (d-6-DMSO δ-4-Acetic, δ values) 1.36 (s, 6H), 1.90 (m, 2H), 3.08 (m, 2H), 3.91 (s, 3H), 3.92 (s, 3H), 4.02 (t, 2H), 6.90 – 7.14 (m, 6H), 7.26 – 7.30 (m, 3H), 7.35 (s, 1H), 7.50 (s, 1H), 7.78 (s, 1H), 8.03 (t, 1H), 8.36 (s, 1H), 8.50 (s, 1H).

Example 21

Preparation of Compound No 21 in Table 5



5 Step 1

This was prepared by an analogous route to that described for example 18 except that 3-(morpholino)propylamine was replaced by 3-(pyrrolid-1-yl)propylamine to produce Intermediate 1, shown above. The product was purified by chromatography. Mass Spectrum m/e 428.5 ($M+H$)⁺.

10 Step 2

The aniline derivative corresponding to intermediate 1 was prepared as described in example 17. **Mass Spectrum** m/e 394.4 ($M+H$)⁺.

Step 3

The aniline derivative of step 2 was converted to compound 21 by reaction with Intermediate 15 D as described in example 17. The product was purified by chromatography.

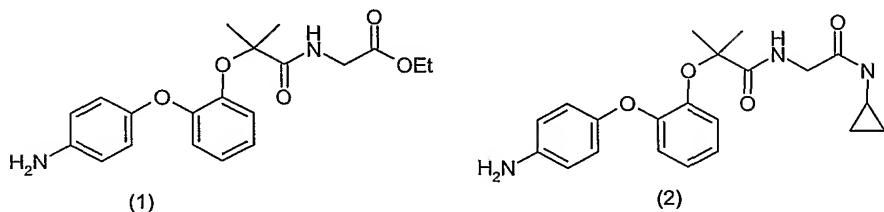
Mass Spectrum m/e 610.2 (M+H)⁺.

NMR Spectrum (d-6-DMSO d-4-Acetic, δ values) 1.36 (s, 6H), 1.74 – 1.99 (m, 6H), 2.89 (m, 2H), 3.00 (m, 2H), 3.16 (m, 2H), 3.46 (m, 2H), 3.98 (s, 6H), 6.94 – 7.01 (m, 3H), 7.04 – 7.20 (m, 3H), 7.42 (s, 2H), 7.46 (s, 1H), 8.03 (t, 1H), 8.16 (s, 1H), 8.94 (s, 1H).

20

Example 22

Preparation of Compound No 22 in Table 5



Step 1

Intermediate 3, example 43, was converted to the corresponding aniline derivative (intermediate (1)) above by reduction at room temperature for 18 hrs in ethyl acetate solution with hydrogen and catalytic 5% Pd/C

5 Mass Spectrum m/e 373.4 (M+H)⁺.

Step 2

Intermediate 1 was then reacted with cyclopropylamine in methanol at room temperature for 18hrs to give intermediate 2.

Mass Spectrum m/e 384.4 (M+H)⁺.

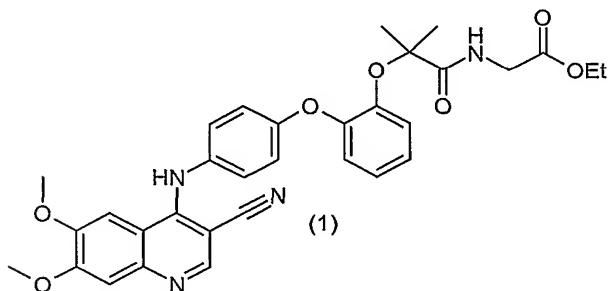
Step 3

Intermediate 2 was the reacted with Intermediate D, described above, in n-propanol in n-propanol solution for 3 hr at 105°C to give compound 22.

Mass Spectrum m/e 594.4 (M+H)⁺.

NMR Spectrum (d-6-DMSO, δ values) 0.39 (m, 2H), 0.42 (m, 2H), 1.36 (s, 6H), 2.63 (m,

15 1H), 3.69 (d, 2H), 4.01 (s, 6H), 7.05 (d, 2H), 7.10 – 7.22 (m, 4H), 7.30 (d, 1H), 7.43 (s, 1H), 7.47 (s, 2H), 7.93 (d, 1H), 8.00 (t, 1H), 8.15 (s, 1H), 8.94 (s, 1H).

Example 23**Preparation of Compound No 23 in Table 5**

20

Step 1

Intermediate 3, example 43, was reacted with Intermediate D, described above, in n-propanol solution for 4 hr at 105°C to produce intermediate 1 in the above scheme.

25 Mass Spectrum m/e 585.4 (M+H)⁺.

Step 2

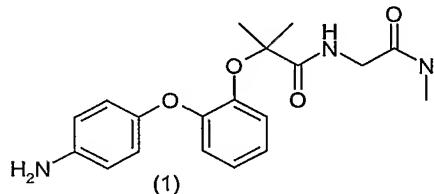
Intermediate 1 was then reacted with cyclopropylamine in ethanol at room temperature for 18hr to give compound 23.

Mass Spectrum m/e 610.2 (M+H)⁺.

NMR Spectrum (d-6-DMSO, δ values) 0.17 (m, 2H), 0.41 (m, 2H), 0.86 (m, 1H), 1.37 (s, 6H), 2.98 (t, 2H), 3.73 (d, 2H), 4.01 (s, 6H), 7.02 – 7.08 (d, 2H), 7.10 – 7.20 (m, 3H), 7.27 (d, 1H), 7.42 – 7.48 (m, 3H), 7.87 (t, 1H), 8.04 (t, 1H), 8.13 (s, 1H), 8.93 (s, 1H).

5 **Example 24**

Preparation of Compound No 24 in Table 5



Step 1

Intermediate 1, example 22, was reacted with methylamine in ethanol at room temperature for 10 18hr to give intermediate (1) in the above scheme.

Mass Spectrum m/e 358.4 (M+H)⁺.

Step 2

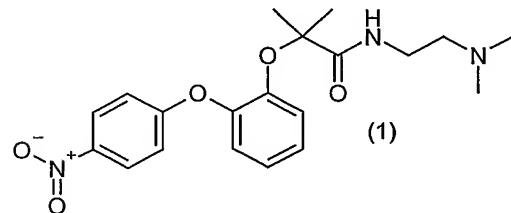
Intermediate 2 was reacted with Intermediate D, described above, in n –propanol solution in 1.0M Ethereal HCl at 105°C for 3hrs.

15 Mass Spectrum m/e 570.20 (M+H)⁺.

NMR Spectrum (d-6-DMSO, δ values) 1.34 (s, 6H), 2.58 (d, 3H), 3.69 (d, 2H), 3.99 (s, 6H), 7.01 (d, 2H), 7.07 – 7.17 (m, 3H), 7.24 (d, 1H), 7.41 (s, 1H), 7.46 (d, 2H), 7.71 (d, 1H), 8.00 (t, 1H), 8.15 (s, 1H), 8.92 (s, 1H).

20 **Example 25**

Preparation of Compound No 25 in Table 5



Step 1

Intermediate 2, example 43, was reacted with oxalyl chloride in DMF/DMC for 16 hr at 0°C

25 followed by reaction with dimethylaminoethylamine in the presence of triethylamine/DCM at

room temperature for 16 hr to give intermediate (1) in the above scheme. The product was purified by chromatography.

Mass Spectrum m/e 388.4 (M+H)⁺.

Step 2

5 Intermediate (1) was converted to the corresponding aniline by reduction at room temperature for 18 hrs in ethyl acetate solution with hydrogen and catalytic 10% Pd/C.

Mass Spectrum m/e 358.5 (M+H)⁺.

Step 3

The product of step 2 was reacted with Intermediate D, described above, in n –propanol

10 solution in 2.0M Ethereal HCl at 105°C for 3hr.

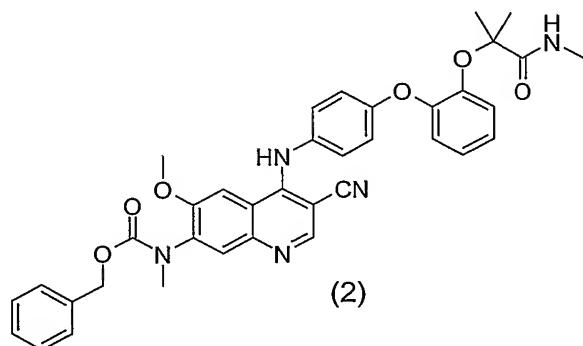
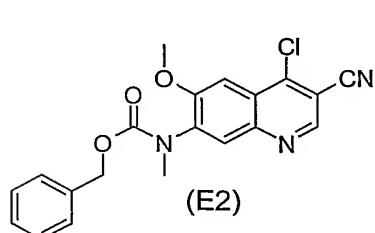
Mass Spectrum m/e 570.5 (M+H)⁺.

NMR Spectrum (d-6-DMSO d-4-Acetic, δ values) 1.36 (s, 6H), 2.72 (m, 6H), 3.10 (m, 2H), 3.47 (m, 2H), 3.98 (s, 3H), 3.99 (s, 3H), 6.92 – 7.19 (m, 6H), 7.38 – 7.48 (m, 3H), 8.13 (m, 2H), 8.89 (s, 1H).

15

Example 26

Preparation of Compound No 26 in Table 5



20 Intermediate (2) above was reacted with 33% HBr in acetic acid for 2hrs to give compound 26.

Mass Spectrum m/e 512.3 (M+H)⁺

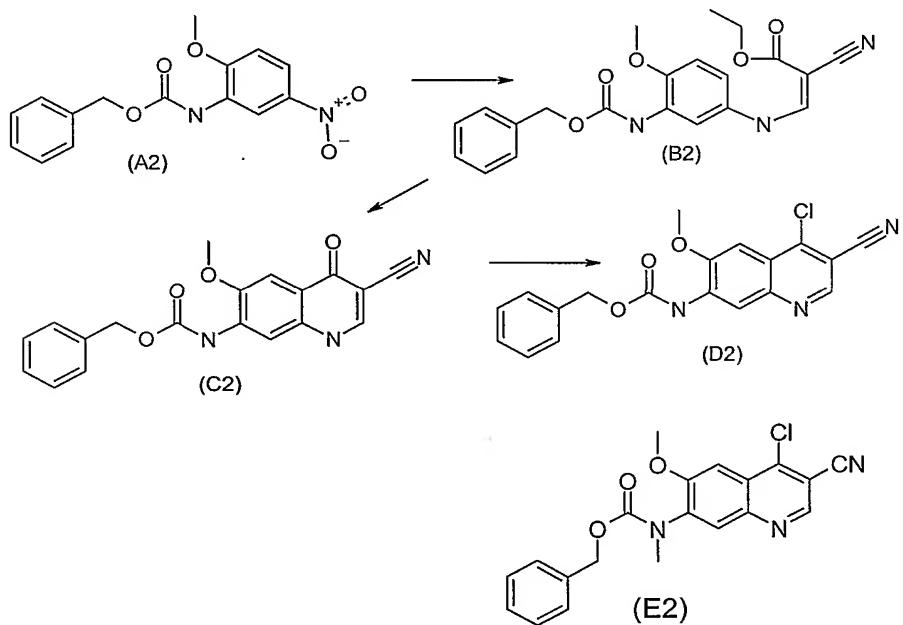
NMR Spectrum (d-6-DMSO, CD₃CO₂D, δ values) 1.32 (s, 6H), 2.60 (s, 3H), 2.86 (s, 3H), 3.99 (s, 3H), 6.65 (s, 1H), 6.97 (d, 3H), 7.09 (m, 3H), 7.40 (d, 2H), 7.81 (s, 1H), 8.83 (s, 1H)

25

Intermediate 2 was prepared by reacting intermediate E2 above with Intermediate D, previously described, in iso-propanol at 100°C for 3.5hr.

Mass Spectrum m/e 646.1 (M+H)⁺

5 Intermediate E2 was prepared as outlined in the following reaction scheme.



10 Step 1

Intermediate (A2) was prepared by reacting benzylchloroformate with 2-methoxy-5-nitroaniline in pyridine at room temperature for 18hr.

NMR Spectrum (d-6-DMSO, δ values) 3.93 (s, 3H), 5.18 (s, 2H), 7.21 (d, 1H), 7.37 (m, 5H), 7.98 (m, 1H), 8.69 (m, 1H), 9.10 (s, 1H).

15 Step 2

Intermediate A2 was reacted in $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ in ethyl acetate at 105°C for 5hrs and then with ethoxyethylcyanoacetate in ethanol at 90°C for 90mins to give intermediate B(2).

NMR Spectrum (d-6-DMSO, δ values) (~3:1 mixture of isomers) 1.22 (m, 3H), 3.76 (s, 3H), 4.16 (m, 2H), 5.13 (s, 2H), 7.02 (m, 2H), 7.35 (m 5H), 7.72 (m, 0.25H), 7.80

20 (m, 0.75H), 8.14 (bs, 0.75H), 8.26 (d, 0.25H), 8.66 (s, 0.25H), 8.71 (s, 0.75H), 10.65 (d, 0.25H), 10.78 (bs, 0.75H).

Step 3

Intermediate (B2) was reacted at 250-260°C for 4hrs with Dowtherm A to give Intermediate (C2).

Mass Spectrum m/e 350 (M+H)⁺.

5 **Step 4**

Intermediate (C2) was reacted at 110°C for 2hrs with methylcyanide in the presence of POCl_3 to give Intermediate (D2). The product was purified by chromatography.

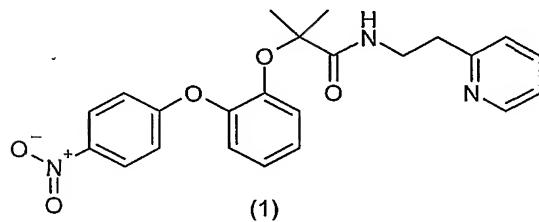
Mass Spectrum m/e 368, 370 (M+H)⁺.

Step 5

10 Intermediate (D2) was converted to intermediate E2 by reaction with KHMDS/MeI/18-Crown-6/DMA at a temperature within the range 0-25°C for 3hrs. The product was purified by chromatography.

Mass Spectrum m/e 382.2 (M+H)⁺

15

Example 27**Preparation of Compound No. 27 in Table 5**20 **Step 1**

Intermediate 2, example 43 was reacted with 2-(pyrid-2-yl)-ethylamine in the presence of DMAP/EDC/DCM at room temperature for 16 hrs. The product was purified by chromatography to produce intermediate (1) in the scheme above.

Mass Spectrum m/e 422.38 (M+H)⁺.

25 **Step 2**

Intermediate (1) was then converted to the corresponding aniline by reduction at room temperature in ethyl acetate solution with hydrogen and catalytic 10% Pd on C at room temperature for 18 hr.

Mass Spectrum m/e 392.5 (M+H)⁺.

Step 3

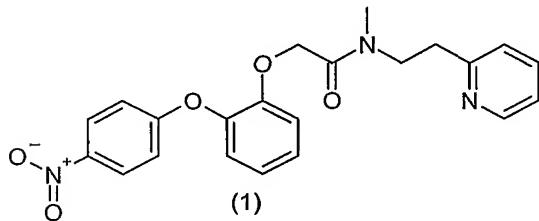
The product of step 2 was then reacted with Intermediate D described above in n-propanol solution in the presence of 2.0M Ethereal HCl 105°C for 3hr. The product was purified by chromatography.

5 Mass Spectrum m/e 604.4 (M+H)⁺.

NMR Spectrum (d-6-DMSO, δ values) 1.26 (s, 6H), 3.14 (m, 2H), 3.57 (m, 2H), 3.98 (s, 3H), 3.99 (s, 3H), 6.88 (d, 1H), 6.96 (d, 2H), 7.05 – 7.14 (m, 3H), 7.43 (d, 2H), 7.49 (s, 1H), 7.68 – 7.77 (m, 2H) 8.07 (t, 1H), 8.23 (s, 1H) 8.27 (t, 1H) 8.71 (d, 1H), 8.92 (s, 1H), 11.26 (bs, 1H).

Example 28

10 Preparation of Compound No. 28 in Table 5

**Step 1**

Intermediate 2, example 43 was reacted with N-[2-(pyrid-2-yl)ethyl] N-(methyl)amine in the presence of DMAP/EDC/DCM at room temperature for 24 hrs. The product was purified by 15 chromatography to produce intermediate (1) in the scheme above.

Mass Spectrum m/e 408.3 (M+H)⁺.

Step 2

Intermediate (1) was then converted to the corresponding aniline by the same method as described in example 27.

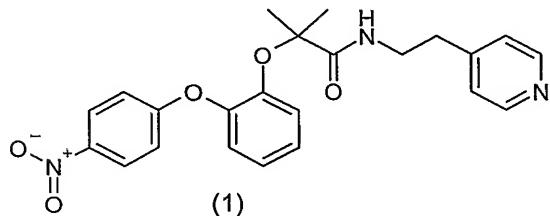
20 Mass Spectrum m/e 378.3 (M+H)⁺.

Step 3

The product of step 2 was then reacted with Intermediate D as described in example 27 except the product was not purified by chromatography.

Mass Spectrum m/e 590.6 (M+H)⁺.

25 NMR Spectrum (d-6-DMSO, δ values) 2.83 + 2.97 (2s, 3H), 3.16 + 3.24 (2t, 2H), 3.69 (t, 2H), 3.99 (s, 6H), 4.77 + 4.80 (2s, 2H), 6.80 – 6.88 (m, 1H), 6.92 – 7.03 (m, 4H), 7.11 (t, 1H), 7.39 (d, 2H), 7.47 (s, 1H), 7.72 – 7.82 (m, 2H) 8.20 (d, 1H), 8.30 (t, 1H) 8.70 (d, 1H), 8.94 (s, 1H), 11.24 (bs, 1H).

Example 29**Preparation of Compound No. 29 in Table 5**

5

Step 1

Intermediate 2, example 43 was reacted with 2-(pyrid-4-yl)-ethylamine in the presence of HOBT/N-Methyl morpholine/EDC/DMA at room temperature for 16 hrs to produce intermediate (1) in the scheme above.

10 Mass Spectrum m/e 422.32 (M+H)⁺.

Step 2

Intermediate (1) was then converted to the corresponding aniline by the method described in example 27

Mass Spectrum m/e 392.4 (M+H)⁺.

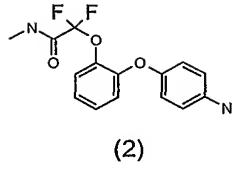
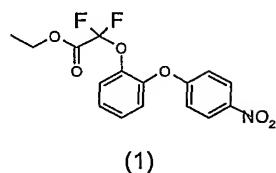
15 **Step 3**

The product of step 2 was then reacted with Intermediate D described by the method described in example 27. The product was purified by chromatography.

Mass Spectrum m/e 604.0 (M+H)⁺.

NMR Spectrum (d-6-DMSO, δ values) 1.29 (s, 6H), 3.05 (m, 2H), 3.52 (m, 2H), 3.99 (s, 3H),

20 4.00 (s, 3H), 6.86 (m, 1H), 6.97 (d, 2H), 7.04 – 7.11 (m, 3H), 7.43 (d, 2H), 7.51 (s, 1H), 7.80 (d, 2H) 8.07 (t, 1H), 8.27 (s, 1H), 8.74 (d, 2H), 8.93 (s, 1H), 11.30 (bs, 1H).

Example 30**Step 1**

5 Intermediate B was reacted with ethyl bromodifluoroacetate and potassium-t-butoxide in the presence of DMA at room temperature for 16 hrs to give intermediate (1).

Mass Spectrum m/e 354.12 (M⁺+H).

Step 2

Intermediate (1) was then converted to the corresponding aniline by reduction for 2 hrs in

10 ethyl acetate solution with hydrogen and catalytic 10% Pd on C

Mass Spectrum m/e 324.2 (M⁺+H).

Step 3

The product of step 2 was then reacted with methylamine in the presence of methanol and ethanol at room temperature for 48 hrs to give intermediate (2) in the above scheme.

15 Mass Spectrum m/e 308.29 (M⁺+H).

Step 4

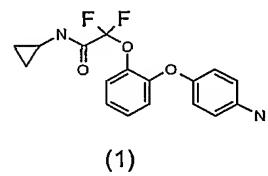
Intermediate (2) was then reacted with Intermediate D, prepared as described above, in n-propanol solution at a temperature of 100°C for 2 hr to give compound 30.

Mass Spectrum m/e 521.07 (M⁺+H).

20 NMR Spectrum (d-6-DMSO, δ values) 2.67(m, 3H), 3.98(s, 6H), 7.02(d, 1H), 7.12(d, 2H), 7.2(t, 1H), 7.28(t, 1H), 7.4(d, 1H), 7.46(d, 2H), 7.5(s, 1H), 8.13(s, 1H), 8.84(br.s, 1H), 8.86(s, 1H), 11.1(br.s, 1H).

Example 31

25 **Preparation of Compound 31 in table 5**



Step 1

Steps 1 –2 of example 30 were followed to give the aniline derivative.

Step 2

The aniline derivative was then reacted with cyclopropylamine in the presence of methanol 5 and ethanol for 48 hrs at room temperature to give intermediate (1) above.

Mass Spectrum m/e 334.3 ($M^+ + H$).

Step 3

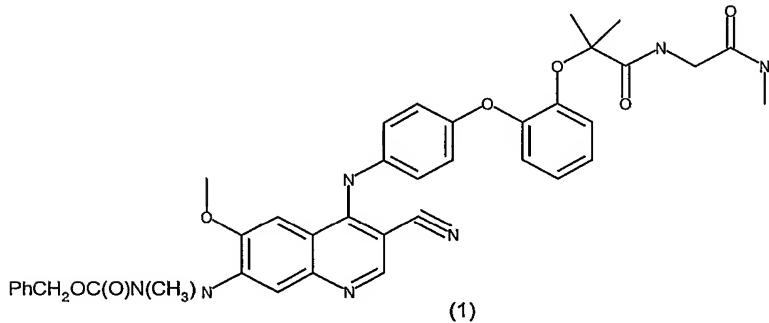
Intermediate (1) was then reacted with Intermediate D, prepared as described above, in n-propanol solution at a temperature of 100⁰C for 2 hr to give compound 31.

10 Mass Spectrum m/e 547.09 ($M^+ + H$).

NMR Spectrum (d-6-DMSO, δ values) 0.55(m, 2H), 0.67(m, 2H), 2.72(m, 1H), 3.96(s, 6H), 7.02(2d, 1H), 7.14(d, 2H), 7.2(t, 1H), 7.29(t, 1H), 7.38(d, 1H), 7.46(d, 2H), 7.51(s, 1H), 8.11(s, 1H), 8.91(s, 1H), 9.03(br.d, 1H), 11.04(v.br.s, 1H).

15 Example 32

Preparation of Compound No. 32 in table 5.

**Step 1**

Intermediate E2, example 26 was reacted with Intermediate (I), example 24 in n-propanol 20 solution at a temperature 105⁰C for 5 hr.

Mass Spectrum m/e 703.3 ($M+H$)⁺

Step 2

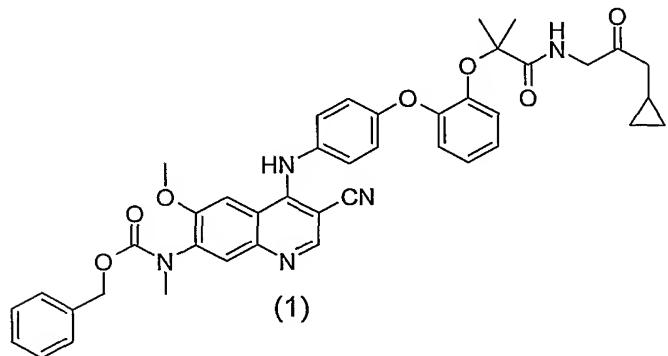
Intermediate (1) above was converted to compound 32 by reaction with thioanisole in 33% HBr at room temperature for 2hr. The product was purified by chromatography.

25 Mass Spectrum m/e 569.19 ($M+H$)⁺

NMR Spectrum (d-6-DMSO + d-4-acetic acid, δ values) 2.56 (s, 6H), 2.84 (s, 3H), 3.68 (s, 3H), 3.95 (s, 3H), 6.68 (s, 1H), 6.95 – 6.98 (m, 3H), 7.06 – 7.12 (m, 4H), 7.19 – 7.22 (d, 1H), 7.29 – 7.32 (d, 2H), 7.73 (s, 1H), 8.55 (s, 1H)

5 Example 33

Preparation of Compound 33 in table 5



Step 1

10 Intermediate E2, example 26 was reacted with intermediate 2, example 22 in n-propanol solution at a temperature 100°C for 1.5 hr to give intermediate (1) above.

Mass Spectrum m/e 729.4 ($M+H$)⁺

Step 2

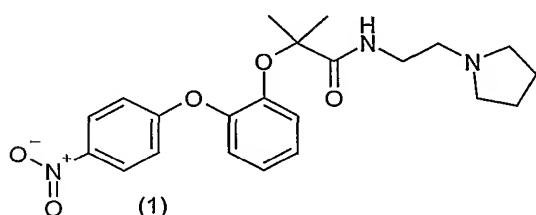
Intermediate (1) was reacted 33% HBr in acetic acid for 2hr to give compound 33.

15 Mass Spectrum m/e 595.2 ($M+H$)⁺

NMR Spectrum (d-6-DMSO, δ values) 0.04 (m, 2H), 0.27 (m, 2H), 1.00 (s, 6H), 2.53 (s, 3H), 3.31 (d, 2H), 3.66 (s, 3H), 6.32 (s, 1H), 6.67 (d, 2H), 6.80 (m, 5H), 7.07 (d, 2H), 7.48 (s, 1H), 7.55 (m, 1H), 7.64 (m, 1H), 8.50 (s, 1H), 10.23 (s, 1H)

20 Example 34

Preparation of compound 34 in table 5



Step 1

Intermediate 2, example 43 was reacted with 2-(pyrrolidin-1-yl)ethylamine in the presence of HOBT/N-Methyl morpholine/EDC/DMA at room temperature for 16hr to give intermediate (1) above.

5 Mass Spectrum m/e 414.4 (M+H)⁺.

Step 2

Intermediate (1) was reduced to the corresponding aniline by reduction in ethyl acetate solution in the presence of hydrogen and catalytic 10% Pd on C at room temperature for 6 hr. Mass Spectrum m/e 384.4 (M+H)⁺.

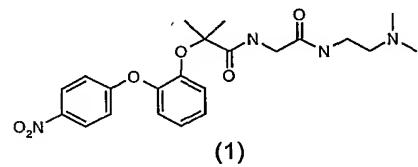
Step 3

The product of step 2 was reacted with intermediate D, prepared as described above, in n-propanol solution in 1.0M Ethereal HCl at a temperature of 105°C for 3hr.

Mass Spectrum m/e 596.3 (M+H)⁺.

NMR Spectrum (d-6-DMSO d-4-Acetic, δ values) 1.36 (s, 6H), 1.88 – 2.00 (m, 4H), 2.95 (m,

15 2H), 3.18 (m, 2H), 3.40 – 3.58 (m, 4H), 3.98 (s, 3H), 3.99 (s, 3H), 6.96 – 7.04 (m, 3H), 7.09 – 7.20 (m, 3H), 7.43 (s, 1H), 7.46 (s, 2H), 8.20 (m, 2H), 8.93 (s, 1H).

Example 35**Preparation of Compound 35 in table 5**

20

Step 1

Intermediate (4), example 43 was reacted with N,N-dimethylethylene diamine in the presence of HOBT/EDC/DCM at room temperature for 16hr to give intermediate (1) above. The product was purified by chromatography.

25 Mass Spectrum m/e 461.3 (M⁺+NH₄).

Step 2

Intermediate (1) was reduced to the corresponding aniline by reduction in ethyl acetate solution in the presence of hydrogen and catalytic Pd on C at room temperature for 3 hr.

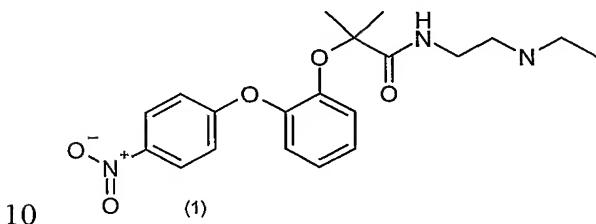
Mass Spectrum m/e 415.4 (M⁺+H).

Step 3

The product of step 2 was reacted with intermediate D, as described above, in n-propanol solution in Ethereal HCl at a temperature of 105°C for 2hr.

Mass Spectrum m/e 625.5 (M⁺-H).

5 NMR Spectrum (d-6-DMSO, δ values) 1.33 (s, 6H), 2.75 (s, 6H), 3.10 (t, 2H), 3.42 (t, 2H), 3.75 (s, 2H), 3.96 (s, 6H), 7.00 (d, 2H), 7.05-7.18 (m, 3H), 7.24 (d, 1H), 7.41 (m, 3H), 8.05 (m, 1H), 8.10-8.20 (m, 2H), 8.89 (s, 1H).

Example 36**Preparation of Compound 36 in table 5****Step 1**

Intermediate (2), example 43 was reacted with 2-(ethylamino)ethylamine in the presence of HOBr/EDC/N-methyl morpholine/DCM at room temperature for 16hr to give intermediate (1) above. The product was purified by chromatography.

15 Mass Spectrum m/e 388.4 (M⁺H)⁺.

Step 2

Intermediate (1) was reduced to the corresponding aniline by reduction in ethyl acetate solution in the presence of ethanol, hydrogen and catalytic 10% Pd on C at room temperature for 6 hr. Mass Spectrum m/e 358.3 (M⁺H)⁺.

Step 3

The product of step 2 was reacted with intermediate D, as described above, in n-propanol solution in 1.0M Ethereal HCl at a temperature of 105°C for 3hr.

Mass Spectrum m/e 568.7 (M⁺H)⁺.

25 NMR Spectrum (d-6-DMSO, δ values) 1.15 (t, 3H), 1.37 (s, 6H), 2.93 (m, 4H), 3.40 (q, 2H), 3.98 (s, 3H), 3.99 (s, 3H), 6.95 – 7.04 (m, 3H), 7.09 – 7.20 (m, 3H), 7.40 (s, 1H), 7.45 (d, 2H), 8.10 (t, 1H), 8.42 (s, 1H), 8.81 (bs, 1H), 8.90 (s, 1H).

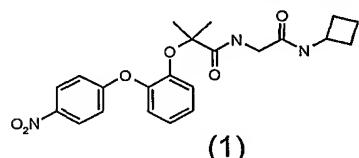
Example 37**Preparation of Compound 37 in Table 5**

The aniline derivative of step 2, example 47 was reacted with Intermediate D, prepared as described above, in n-propanol solution at a temperature of 105°C for 2hr to give compound 5 37.

Mass Spectrum m/e 584.2 (M⁺+H).

NMR Spectrum (d-6-DMSO, δ values) 0.99 (t, 3H), 1.34 (s, 6H), 3.07 (m, 2H), 3.69 (d, 2H), 3.98 (s, 6H), 7.00 (d, 2H), 7.05-7.18 (m, 3H), 7.22 (d, 1H), 7.40-7.46 (m, 3H), 7.76 (t, 1H), 7.99 (t, 1H), 8.14 (s, 1H), 8.91 (s, 1H)

10

Example 38**Preparation of Compound 38 in Table 5****Step 1**

15 Intermediate (4), example 43 was reacted with cyclobutylamine in the presence of DMAP/EDC/DCM at room temperature for 16hr to give intermediate (1) above. The product was purified by chromatography.

Mass Spectrum m/e 426 (M⁺-H).

Step 2

20 Intermediate (1) was reduced to the corresponding aniline by reduction in ethyl acetate solution in the presence of hydrogen and catalytic Pd on C at room temperature for 3 hr.

Mass Spectrum m/e 398.3 (M⁺+H).

Step 3

25 The product of step 2 was reacted with intermediate D, prepared as described above, in n-propanol solution at a temperature of 100°C for 2hr.

Mass Spectrum m/e 610.3 (M⁺+H).

NMR Spectrum (d-6-DMSO, δ values) 1.34 (s, 6H), 1.60 (m, 2H), 1.83 (m, 2H), 2.12 (m, 2H), 3.65 (d, 2H), 3.98 (s, 3H), 3.99 (s, 3H), 4.18 (m, 1H), 7.00 (d, 2H), 7.05-7.18 (m, 3H), 7.23 (d, 1H), 7.35-7.43 (m, 3H), 7.94-8.08 (m, 3H), 8.85 (s, 1H)

Example 39**Preparation of Compound 39 in Table 5****Step 1**

5 4-methoxybenzamine was reacted with ethyl(ethoxymethylene)cyanoacetate in ethanol at 95°C for 2hr and produced intermediate ethyl 3-(4-methoxyphenylamino) 2-cyanoprop-2-enylcarboxylate.

Mass Spectrum m/e 245.17 (M-H)⁻

Step 2

10 Intermediate 2 was reacted with Dowtherm at 260°C to give 3-cyano, 4-oxo, 6-methoxy dihydroquinoline.

Mass Spectrum m/e 199.3 (M-H)⁻

Step 3

15 3-cyano, 4-oxo, 6-methoxy dihydroquinoline was reacted with phosphorus oxychloride in acetonitrile at 85°C for 5hr to give 3-cyano, 4-chloro, 6-methoxy quinoline 97% purity by HPLC

Step 4

3-cyano, 4-chloro, 6-methoxy quinoline was reacted with Intermediate C, prepared as described above, in n-propanol solution at 105°C/3hr to give compound 39.

20 Mass Spectrum m/e 483.19 (M+H)⁺

NMR Spectrum (d-6-DMSO, δ values) 1.33 (s, 6H), 2.62 (d, 3H), 3.97 (s, 3H), 6.98 – 7.15 (m, 6H), 7.43 – 7.46 (d, 2H), 7.65 – 7.70 (m, 1H), 7.78 (m, 1H), 7.97 – 8.00 (d, 1H), 8.20 (m, 1H), 8.93 (s, 1H), 11.18 (bs, 1H) es

25 **Example 40**

Preparation of Compound 40 in Table 5**Step 1**

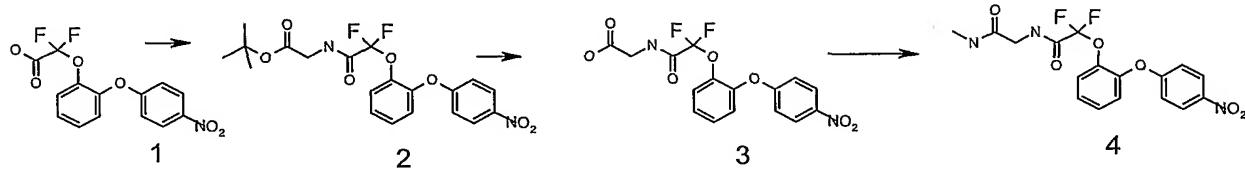
30 3-cyano, 4-chloro, 6-methoxy quinoline, prepared as described in example 39, was reacted with intermediate 1, example 24 in n-propanol solution at a temperature of 105°C for 2hr to give compound 40.

Mass Spectrum m/e 540.19 (M+H)⁺

NMR Spectrum (d-6-DMSO, δ values) 1.35 (s, 6H), 2.58 (d, 3H), 3.70 (d, 2H), 3.97 (s, 3H), 7.01 – 7.04 (d, 2H), 7.10 – 7.16 (m, 3H), 7.22 – 7.25 (d, 2H), 7.42 – 7.45 (d, 2H), 7.67 – 7.71 (m, 2H), 7.97 – 8.03 (m, 2H), 8.19 (m, 1H), 8.92 (s, 1H).

5 Example 41

Preparation of Compound 41 in Table 5



Step 1

10 Intermediate (1), example 30 was reacted with sodium hydroxide in methanol in water for 48 hrs to produce intermediate (1) in the above scheme.

Step 2

Intermediate 1 was reacted with glycine-t-butylester in the presence of HCl/EDC/DMAP/Dichloromethane at room temperature for 16 hrs to give intermediate (2)

15 Mass Spectrum m/e 411.09 ($M^+ + H$).

Step 3

Intermediate (2) was reacted with TFA/Triethylsilane/Dichloromethane at room temperature for 16 hrs to give intermediate (3).

NMR Spectrum (d-6-DMSO, δ values) 3.77(d, 2H), 7.09(d, 2H), 7.3-7.46(m, 3H), 7.5(d, 1H),

20 8.22(d, 2H), 9.25(t, 1H), 12.55(v.br.s, 1H).

Step 4

Intermediate (3) was reacted with methylamine in the presence of HCl/EDC/DMAP/Dichloromethane at room temperature for 16 hrs to give intermediate (4)

NMR Spectrum (d-6-DMSO, δ values) 2.56(d, 3H), 3.66(d, 2H), 7.08(d, 2H),

25 7.27-7.46(m, 3H), 7.5(d, 1H), 7.83(br.q, 1H), 8.21(d, 2H), 9.02(br.t, 1h).

Step 5

Intermediate (4) was reduced to the corresponding aniline by reduction in ethyl acetate solution in the presence of hydrogen and catalytic 5%Pd on C at room temperature for 2 hrs.

Mass Spectrum m/e 366.18 (M^+H).

Step 6

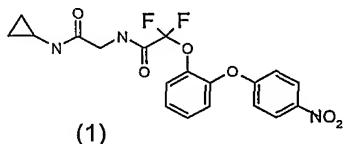
The product of step 5 was reacted with intermediate D, prepared as described above, in n-propanol solution at a temperature of 100°C for 2hr.

5 Mass Spectrum m/e 578.09 (M^+H).

NMR Spectrum (d-6-DMSO, δ values) 2.59(d, 3H), 3.74(d, 2H), 3.97(s, 6H), 7.04(d, 1H), 7.14(d, 2H), 7.2(t, 1H), 7.29(t, 1H), 7.43(s, 1H), 7.45(d, 1H), 7.5(d, 2H), 7.9(br.q, 1H), 8.1(s, 1H), 8.9(s, 1H), 9.1(br.t, 1H), 11.0(v.br.s, 1H).

10 **Example 42**

Preparation of Compound 42 in Table 5



Step 1

15 Intermediate (3), example 41 was reacted with cyclopropylamine in the presence of EDC/DMAP/Dichloromethane at room temperature for 16 hrs to give intermediate (1) above. NMR Spectrum (d-6-DMSO, δ values) 0.43(m, 2H), 0.65(d, 2H), 2.48(m, 1H), 3.66(d, 2H), 7.08(d, 2H), 7.27-7.46(m, 3H), 7.5(d, 1H), 8.08(br.d, 1H), 8.21(d, 2H), 9.04(br.t, 1h).

Step 2

20 Intermediate (1) was reduced to the corresponding aniline by reduction in ethyl acetate solution in the presence of hydrogen and catalytic 5%Pd on C for 2 hrs.

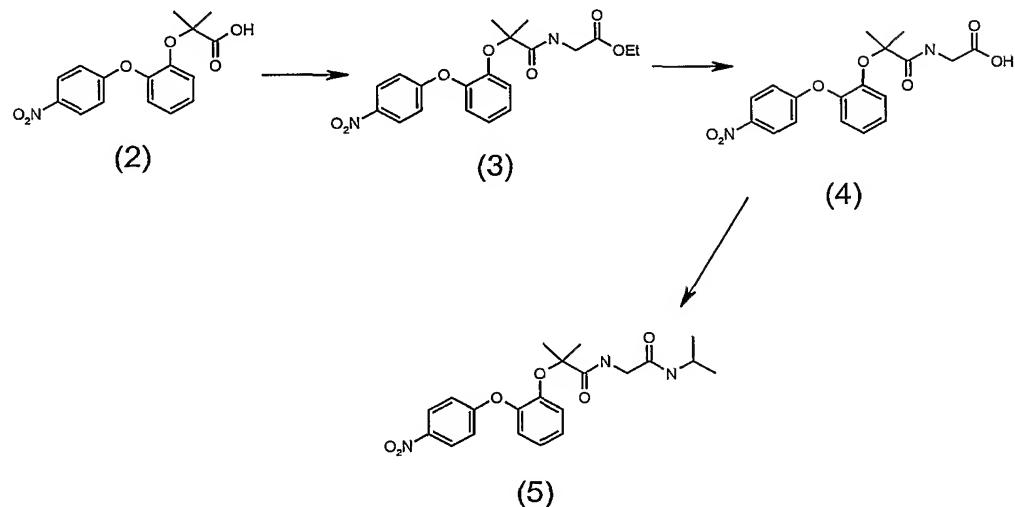
Mass Spectrum m/e 392.16 (M^+H).

Step 3

The product of step 2 was reacted with intermediate D, prepared as described above, in n-propanol solution at a temperature of 100°C for 2hr.

Mass Spectrum m/e 604.11 (M^+H).

NMR Spectrum (d-6-DMSO, δ values) 0.42(m, 2H), 0.64(m, 2H), 2.64(m, 1H), 3.74(d, 2H), 3.97(s, 6H), 7.04(d, 1H), 7.14(d, 2H), 7.2(t, 1H), 7.29(t, 1H), 7.43(d, 1H), 7.45(s, 1H), 7.5(d, 2H), 7.9(br.d, 1H), 8.1(s, 1H), 8.9(s, 1H), 9.1(br.t, 1H), 11.1(v.br.s, 1H).

Example 43**Preparation of Compound No. 43 in Table 5****5 Step 1**

Intermediate B1, described above, was reacted with sodium hydroxide in methanol at room temperature for 16hrs to form the corresponding hydroxide

Mass Spectrum m/e 316.4 (M^-H).

Step 2

10 The product of step 1 was then reacted with glycine ethyl ester in DMAP/EDAC at room temperature for 16hrs to give Intermediate (3). The product was purified by chromatography.

Mass Spectrum m/e 425.1 (M^++Na).

Step 3

15 Intermediate (3) was converted to the corresponding hydroxide (intermediate 4) by reaction with sodium hydroxide in the presence of methanol at room temperature for 16hrs.

Mass Spectrum m/e 375.2 (M^++H).

Step 5

Intermediate 4 was converted to intermediate 5 reaction with isopropylamine in DMAP/EDAC at room temperature for 16hr. The product was purified by chromatography.

Mass Spectrum m/e 416.2 (M^++H).

Step 6

Intermediate 5 was then converted to the corresponding aniline by reduction at room temperature for 16 hrs in ethyl acetate solution with hydrogen and catalytic 5% Pd/C. Mass Spectrum m/e 386.4 ($M^+ + H$).

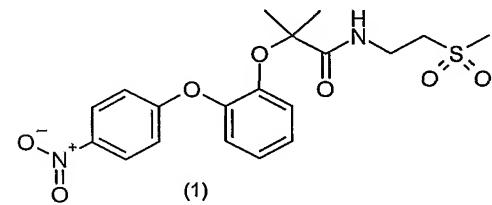
5 **Step 7**

Intermediate 6 was reacted with Intermediate D in n-propanol solution for 3 hr at 105°C to produce the compound no.43.

Mass Spectrum m/e 598.3 ($M^+ + H$).

NMR Spectrum (d-6-DMSO, δ values) 1.02 (d, 6H), 1.35 (s, 6H), 3.68 (d, 2H), 3.80 (m, 1H),

10 3.98 (s, 3H), 3.99 (s, 3H), 7.00 (d, 2H), 7.05-7.19 (m, 3H), 7.22 (d, 1H), 7.42 (d, 2H), 7.54 (s, 1H), 7.67 (d, 1H), 7.98 (t, 1H), 8.23 (s, 1H), 8.94 (s, 1H).

Example 44**Preparation of Example 44 in table 5****Step 1**

Intermediate (2) example 43 was reacted with 2-(methanesulphonyl)ethylamine in DMAP/EDC/DCM at room temperature for 18hr to give intermediate (1) above. The product was purified by chromatography.

20 Mass Spectrum m/e 423.3 ($M^+ + H$).

Step 2

Intermediate 1 was then converted to the corresponding aniline by reduction at room temperature for 16 hrs in ethyl acetate solution with hydrogen and catalytic 5% Pd/C. The product was purified by chromatography.

25 Mass Spectrum m/e 393.3 ($M^+ + H$).

Step 3

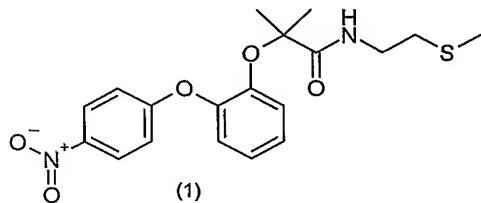
The product of step 2 was then reacted with Intermediate D in n-propanol solution for 3 hr at 105°C to produce the compound no.44.

Mass Spectrum m/e 605.3 ($M^+ + H$).

NMR Spectrum (d-6-DMSO, δ values) 1.24 (s, 6H), 2.96 (s, 3H), 3.25 (t, 2H), 3.52 (q, 2H), 3.98 (s, 6H), 6.96 – 7.18 (m, 6H), 7.39 – 7.46 (m, 3H), 8.10 – 8.19 (m, 2H), 8.90 (s, 1H).

Example 45

5 Preparation of Compound No. 45 in table 5



Step 1

10 Intermediate (2) example 43 was reacted with 2-(methylthio)ethylamine in DMAP/EDC/DCM at room temperature for 18hr to give intermediate (1) above. The product was purified by chromatography.
Mass Spectrum m/e mass ion not observed $(M+H)^+$.
NMR Spectrum (d-6-DMSO, δ values) 1.24 (s, 6H), 2.00 (s, 3H), 2.46 (t, 2H), 3.21 (q, 2H), 7.00 – 7.08 (m, 3H), 7.14 (t, 1H), 7.26 (t, 2H), 7.88 (t, 1H), 8.23 (d, 2H).

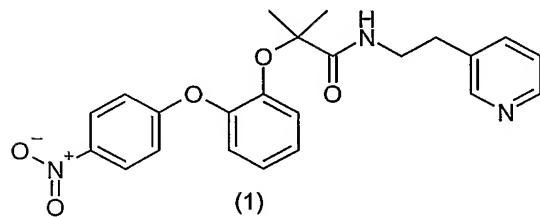
Step 2

Intermediate 1 was then converted to the corresponding aniline by reduction at room temperature for 16 hrs in ethyl acetate solution with hydrogen and catalytic 5% Pd/C. Mass Spectrum m/e 361.3 $(M+H)^+$.

20 Step 3

The product of step 2 was then reacted with Intermediate D in n-propanol solution for 3 hr at 105°C to produce the compound no.45.

Mass Spectrum m/e 573.3 $(M+H)^+$.
NMR Spectrum (d-6-DMSO, δ values) 1.35 (s, 6H), 2.03 (s, 3H), 2.51 (t, 2H), 3.28 (q, 2H), 3.98 (s, 6H), 6.97 – 7.18 (m, 6H), 7.38 – 7.46 (m, 3H), 7.99 (t, 1H), 8.12 (s, 1H), 8.90 (s, 1H).

Example 46**Preparation of Compound No. 46 in table 5****Step 1**

5 Intermediate 2, example 43 was reacted with 2-(pyrid-3-yl)-ethylamine in the presence of HOBT/N-Methyl morpholine/EDC/DMA at room temperature for 16 hr to produce intermediate (1) in the scheme above.

Mass Spectrum m/e 422.3 (M+H)⁺.

Step 2

10 Intermediate (1) was then converted to the corresponding aniline by reduction at room temperature in ethyl acetate solution with hydrogen and catalytic 10% Pd on C at room temperature for 36 hr.

Mass Spectrum m/e 392.3 (M+H)⁺.

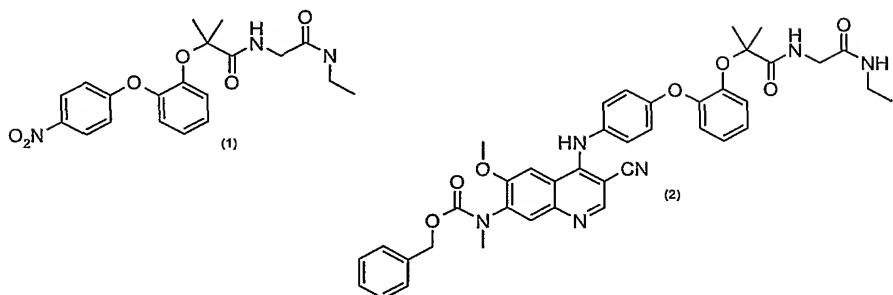
Step 3

15 The product of step 2 was then reacted with Intermediate D described above in n-propanol solution in the presence of 1.0M Ethereal HCl at 105°C for 3hr. The product was purified by chromatography.

Mass Spectrum m/e 604.3 (M+H)⁺.

NMR Spectrum (d-6-DMSO, δ values) 1.26 (s, 6H), 2.94 (t, 2H), 3.47 (q, 2H), 3.98 (s, 3H),

20 3.99 (s, 3H), 6.86 (d, 1H), 6.96 (d, 2H), 7.05 – 7.14 (m, 3H), 7.42 (d, 2H), 7.49 (s, 1H), 7.60 (m, 1H) 8.00 (t, 1H), 8.21 – 8.27 (m, 2H), 8.67 – 8.71 (m, 2H), 8.92 (s, 1H), 11.22 (bs, 1H).

Example 47**Preparation of Compound No. 47 in table 5****5 Step 1**

Intermediate 4, example 43 with ethylamine hydrochloride/EDC/ at room temperature for 16hr to give intermediate (1) above

Mass Spectrum m/e 402.3 (M+H)⁺

Step 2

10 Intermediate 1 was then converted to the corresponding aniline by reduction at room temperature for 3 hrs in ethyl acetate solution with hydrogen and catalytic Pd/C.

Mass Spectrum m/e 370.5 (M-H)⁻

Step 3

15 The product of step 2 was reacted with Intermediate D, prepared as described above, in n-15 propanol solution for 2 hr at 100°C to produce intermediate (2)

Mass Spectrum m/e 717.3 (M+H)⁺

Step 3

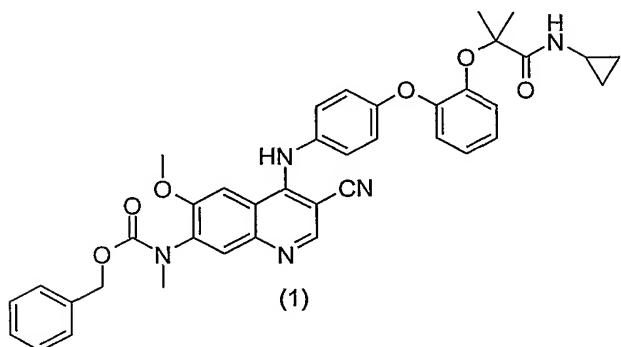
Intermediate (2) was reacted with 33% HBr in acetic acid for 2hr.

Mass Spectrum m/e 583.2 (M+H)⁺

20 NMR Spectrum (d-6-DMSO, CD₃CO₂D, δ values) 0.97 (t, 3H), 1.35 (s, 6H), 2.85 (s, 3H), 3.07 (q, 2H), 3.68 (m, 2H), 4.00 (s, 3H), 6.67 (s, 1H), 7.00 (d, 2H), 7.10 (m, 3H), 7.22 (d, 1H), 7.38 (d, 2H), 7.83 (s, 1H), 7.96 (m, 1H), 8.81 (s, 1H)

Example 48

Preparation of Compound 48 in table 5



Step 1

5 Intermediate E2, example 26 was reacted with Intermediate F in n-propanol at 100°C for 2hr to give intermediate (1) above

Mass Spectrum m/e 672.3 (M+H)⁺

Step 2

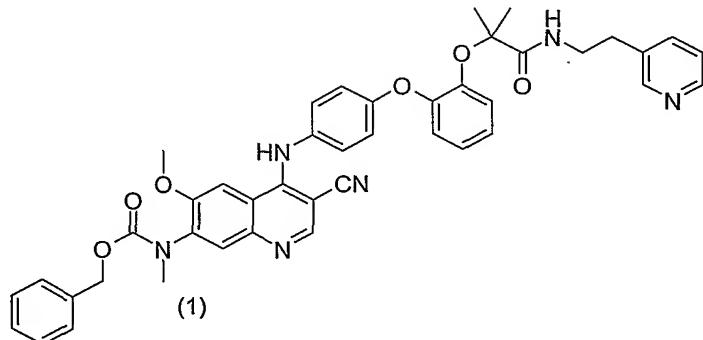
Intermediate (1) was reacted in 33% HBr in acetic acid for 2hrs to give compound 48. The compound was purified by chromatography.

Mass Spectrum m/e 538.3 (M+H)⁺

NMR Spectrum (d-6-DMSO, δ values) 0.05 (m, 2H), 0.20 (m, 2H), 0.93 (s, 6H), 2.30 (m, 1H), 2.47 (q, 3H), 3.61 (s, 3H), 6.31 (s, 1H), 6.57 (m, 3H), 6.66 (m, 1H), 6.77 (m, 1H), 7.00 (d, 2H), 7.48 (m, 2H), 7.48 (m, 2H), 8.40 (s, 1H), 10.25 (s, 1H)

15 Example 49

Preparation of Compound No. 49 in table 5



Step 1

The aniline derivative of step 2 of example 46 was reacted with Intermediate 2, example 26 in n-propanol at 100°C for 105 min to give intermediate (1) above

Mass Spectrum m/e 737.7 (M+H)⁺

5 **Step 2**

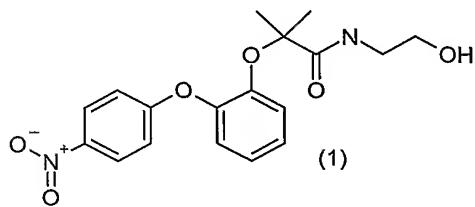
Intermediate (1) was then reacted in 33% HBr in acetic acid for 2hrs to give compound 49.

Mass Spectrum m/e 603.3 (M+H)⁺

NMR Spectrum (d-6-DMSO, CD₃CO₂D, δ values) 1.25 (s, 6H), 2.85 (s, 3H), 2.92 (t, 2H),

3.46 (m, 2H), 4.00 (s, 3H), 6.70 (s, 1H), 6.83 (d, 1H), 6.95 (d, 2H), 7.07 (m, 3H), 7.39 (m,

10 3H), 7.76 (m, 1H), 7.91 (m, 1H), 8.02 (m, 1H), 8.19 (m, 1H), 8.67 (m, 2H), 8.80 (s, 1H)

Example 50**Preparation of compound No. 50 in table 5**15 **Step 1**

Intermediate 2, example 43 was reacted with 2-(hydroxy)ethylamine in the presence of DMAP/EDC/DMA at room temperature for 18 hrs to produce intermediate (1) in the scheme above.

Mass Spectrum m/e 361.3 (M+H)⁺.

20 **Step 2**

Intermediate (1) was then converted to the corresponding aniline by reduction at room temperature in ethyl acetate solution with hydrogen and catalytic 5% Pd on C at room temperature for 18 hr.

Mass Spectrum m/e 333.1 (M+H)⁺.

25 **Step 3**

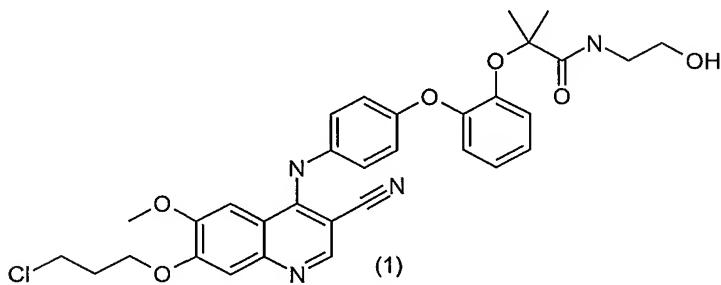
The product of step 2 was then reacted with Intermediate D, prepared as described above, in n-propanol solution at 105°C for 3hr to give compound 50.

Mass Spectrum m/e 543.3 (M+H)⁺.

NMR Spectrum (d-6-DMSO d-4-Acetic, δ values) 1.34 (s, 6H), 3.16 (q, 2H), 3.39 (t, 2H), 3.99 (s, 6H), 6.97 – 7.18 (m, 6H), 7.41 (s, 1H), 7.44 (s, 2H), 7.76 (t, 1H), 8.15 (s, 1H), 8.90 (s, 1H).

5 **Example 51**

Preparation of Compound 51 in table 5



Step 1

Intermediate (1), example 50 was reacted with Intermediate (A) in n-propanol solution at 10 105°C for 3.5hr to give intermediate (1) above.

Mass Spectrum m/e 605.3 ($M+H$)⁺

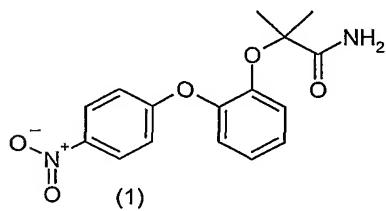
Step 2

Intermediate (1) was reacted with n-morpholine in sodium iodide at room temperature for 3 days to give compound 51. The product was purified by chromatography. Mass Spectrum m/e 15 656.3 ($M+H$)⁺

NMR Spectrum (d-6-DMSO d-4-Acetic, δ values) 1.34 (s, 6H), 2.31 (m, 2H), 3.10 (m, 2H), 3.17 (t, 2H), 3.29 (t, 2H), 3.38 (t, 2H), 3.48 (m, 2H), 3.80 (m, 2H), 3.95 (m, 2H), 3.99 (s, 3H), 4.30 (t, 2H), 6.97 – 7.17 (m, 6H), 7.41 (d, 2H), 7.46 (s, 1H), 7.71 (t, 1H), 8.12 (s, 1H), 8.90 (s, 1H).

20 **Example 52**

Preparation of compound 52 in table 5



Step 1

Intermediate B1, prepared as described above, was reacted with formamide in the presence of 5% NaOMe in MeOH/DMA at 100°C for 1 hr to give intermediate (1). The product was purified by chromatography.

5 Mass Spectrum m/e 315 (M-H)⁻.

Step 2

Intermediate (1) was then converted to the corresponding aniline by reduction at room temperature in ethyl acetate solution with hydrogen and catalytic 5% Pd on C at room temperature for 3 hr.

10 Mass Spectrum m/e 287.2 (M+H)⁺.

Step 3

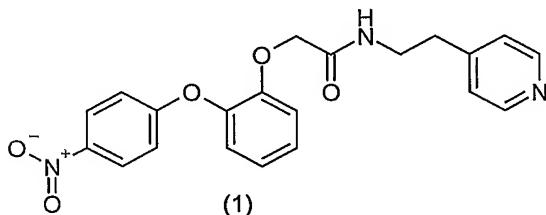
The product of step 2 was then reacted with Intermediate D, prepared as described above, in n-propanol solution at 105°C for 3hr to give compound 52.

Mass Spectrum m/e 499.2 (M+H)⁺.

15 NMR Spectrum (d-6-DMSO, δ values) 1.34 (s, 6H), 3.98 (s, 6H), 6.97 – 7.19 (m, 6H), 7.25 (d, 2H), 7.39 – 7.46 (m, 3H), 8.12 (s, 1H), 8.90 (s, 1H), 11.02 (bs, 1H).

Example 52A**Preparation of compound 52A in table 5**

20

**Step 1**

4-(fluoro)nitrobenzene was reacted with 2-(2-hydroxyphenoxy)acetic acid in the presence of 25 potassium t-butoxide/DMA at 150°C for 2hrs to give 2-[(2-(4-nitrophenoxy)phenoxy] acetic acid. The product was purified by chromatography.

Mass Spectrum m/e 288 (M-H)⁻

Step 2

The product of step 1 was reacted with 2-(pyrid-4-yl)-ethylamine in the presence of N-methyl morpholine /HOBT/EDC/DCM at room temperature for 16 hrs to produce intermediate (1) above.

5 Mass Spectrum m/e 394.3 (M+H)⁺.

Step 3

Intermediate (1) was then converted to the corresponding aniline by reduction at room temperature in ethyl acetate solution with hydrogen and catalytic 10% Pd on C at room temperature for 18 hr.

10 Mass Spectrum 364.3 (M+H)⁺.

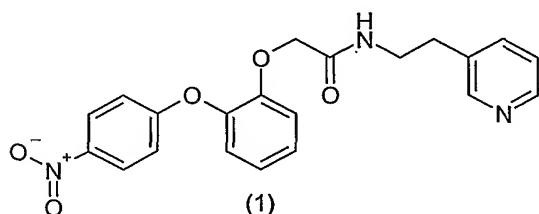
Step 4

The product of step 3 was then reacted with Intermediate D, prepared as described above, in n-propanol solution in the presence of 1.0M Ethereal HCl 105°C for 3hr to give compound 52A.

15 Mass Spectrum m/e 576.3 (M+H)⁺.

NMR Spectrum (d-6-DMSO, δ values) 3.01 (t, 2H), 3.50 (q, 2H), 3.98 (s, 3H), 3.99 (s, 3H), 4.44 (s, 2H), 6.95 – 7.05 (m, 4H), 7.13 (m, 1H), 7.41 (d, 2H), 7.50 (s, 1H), 7.83 (d, 2H), 7.90 (t, 1H) 8.24 (s, 1H), 8.74 (d, 2H), 8.92 (s, 1H).

20 Example 52B

Preparation of Compound No. 52B in table 5**Step 1**

25 2[(2-(4-nitrophenoxy)phenoxy] acetic acid from example 52A was reacted with 2-(pyrid-3yl)-ethylamine in the presence of N-methyl morpholine /HOBT/EDC/DCM at room temperature for 3 days produce intermediate (1) above.

Mass Spectrum m/e 394.3 (M+H)⁺.

Step 2

Intermediate (1) was then converted to the corresponding aniline by reduction at room temperature in ethyl acetate solution with hydrogen and catalytic 10% Pd on C at room temperature for 16 hr.

5 Mass Spectrum 364.3 ($M+H$)⁺.

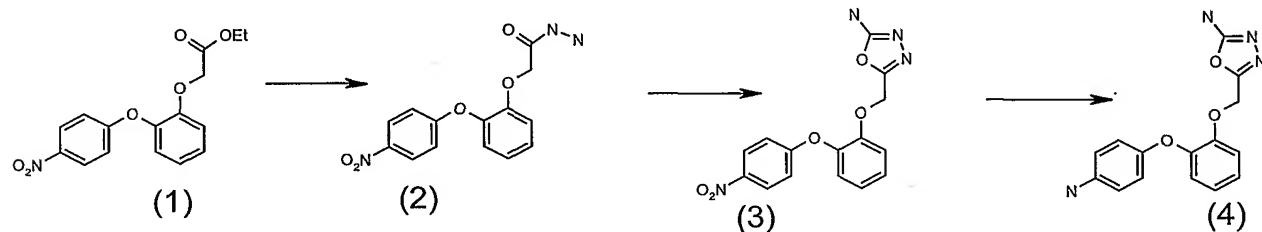
Step 3

The product of step 2 was then reacted with Intermediate D, prepared as described above in n-propanol solution in the presence of 2.0M Ethereal HCl 105°C for 3hr to give compound 52B. Mass Spectrum m/e 576.3 ($M+H$)⁺.

10 NMR Spectrum (d-6-DMSO, δ values) 2.92 (t, 2H), 3.46 (q, 2H), 3.98 (s, 6H), 4.44 (s, 2H), 6.95 – 7.06 (m, 4H), 7.15 (t, 1H), 7.41 (d, 2H), 7.48 (s, 1H), 7.78 – 7.89 (m, 2H) 8.20 (s, 1H), 8.26 (d, 1H), 8.70 (d, 1H), 8.74 (s, 1H), 8.91 (s, 1H).

Example 52C

15 Preparation of Compound 52C in table 5

**Step 1**

Intermediate B, prepared as described above, was reacted with ethyl bromoacetate in the presence of K_2CO_3 and acetone and refluxed for 18hr to give intermediate (1) in the above scheme. The product was purified by chromatography.

Mass Spectrum m/e 316 ($M-H$)

Step 2

Intermediate (1) was then reacted with hydrazine hydrate in ethanol and refluxed for 6.5hr to give intermediate (2). The product was purified by chromatography.

Mass Spectrum m/e 304 (M^++H)

Step 3

Intermediate (2) was reacted with cyanogen bromide in the presence of dioxane and $NaHCO_3$ for 5.5hr to give intermediate (3).

Mass Spectrum m/e 329 ($M^+ + H$)

Step 4

Intermediate (3) was then converted to the corresponding aniline by reduction at room temperature in ethyl acetate solution with hydrogen and catalytic % Pd on C at room temperature for 18 hr. The product was purified by chromatography.

Mass Spectrum m/e 299 ($M^+ + H$)

Step 5

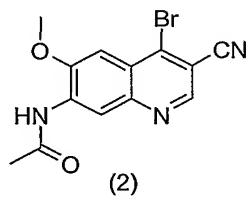
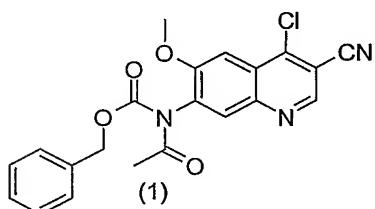
The product of step 4 was then reacted with Intermediate D, prepared as described above in n-propanol solution at 110°C for 18hr to give compound 52C.

10 Mass Spectrum m/e 511 ($M^+ + H$)

NMR Spectrum (d-6-DMSO, δ values) 4.0 (s, 6H), 5.15 (s, 2H), 7.0 (d, 2H), 7.0 (s, 2H), 7.15 (m, 3H), 7.3 (d, 1H), 7.4 (d, 2H), 7.45 (s, 1H), 8.2 (s, 1H), 8.9 (s, 1H), 11.2 (br s, 1H)

Example 52D

15 Preparation of Compound 52D in table 5



20 Step 1

Intermediate D2, example 26 was reacted with KHMDS/Ac₂O/18-Crown-6/THF ar room temperature for 150min to give intermediate (1) above.

Mass Spectrum m/e 410.2 ($M + H$)⁺

Step 2

25 Intermediate (1) was reacted with 33% HBr in acetic acid for 2hr to give intermediate (2) above.

Mass Spectrum m/e 322.1 ($M + H$)⁺

Step 3

Intermediate (2) was reacted with intermediate (1), example 24 in n-propanol solution at 100°C for 2hr to give compound 52D..

Mass Spectrum m/e 597.5 (M+H)⁺

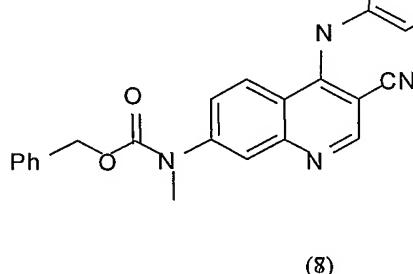
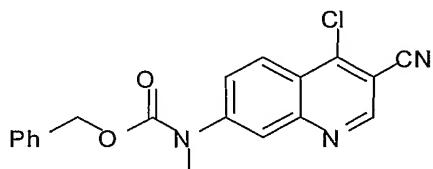
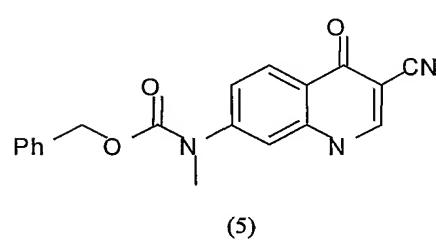
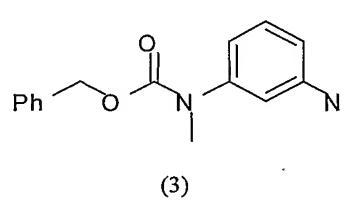
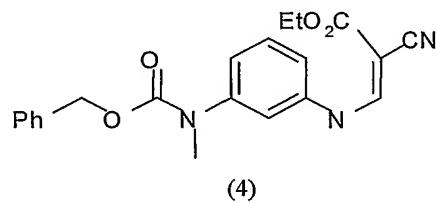
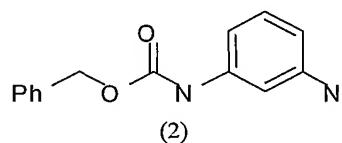
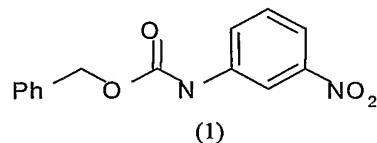
NMR Spectrum (d-6-DMSO, δ values) 1.34 (s, 6H), 2.24 (s, 3H), 2.58 (d, 3H), 3.68 (d, 2H), 4.05 (s, 3H), 7.04 (d, 2H), 7.10 (m, 3H), 7.22 (d, 1H), 7.43 (d, 2H), 7.69 (m, 1H), 8.01 (t, 1H), 8.08 (s, 1H), 8.90 (d, 2H), 9.84 (s, 1H), 10.81 (bs, 1H)

5

Example 53

Preparation of Compound 53 in table 6

This compound was prepared as outlined in the following reaction scheme.



Step 1

Intermediate (1) was prepared by reacting nitroaniline with benzyl chloroformate pyridine in the presence of pyridine at room temperature for 20hr.

Mass Spectrum m/e 271.4 (M-H)⁻

5 Step 2

Intermediate (1) was reacted with Fe/glacial acetic acid/ethanol/water at 100°C for 1.75hr to give intermediate (2). The product was purified by chromatography.

Mass Spectrum m/e 243.3 (M+H)⁺

Step 3

10 Intermediate (2) was reacted in KHMDS/MeI/18-crown-6 ether/THF at a temperature within the range 0°C-25°C for 1.5hr to give intermediate (3). The product was purified by chromatography.

Mass Spectrum m/e 257.3 (M+H)⁺

Step 4

15 Intermediate (3) was reacted with ethyl(ethoxymethylene)cyanoacetate in the presence of ethanol at 95°C for 4hr to give intermediate (4).

Mass Spectrum m/e 380.3 (M+H)⁺

Step 5

Intermediate (4) was reacted with Dowtherm at 260°C for 4hr to give intermediate (5). Mass

20 Spectrum m/e 334.2 (M+H)⁺

Step 6

Intermediate (5) was converted to intermediate (6) by reaction with POCl₃ in acetonitrile conditions at 85°C for 1.5hr.

Mass Spectrum m/e 352.2 (M+H)⁺

25 Step 7

Intermediate 6 was reacted with Intermediate C, prepared as described above, in n-propanol solution at 105°C for 2hr.

Mass Spectrum m/e 616.4 (M+H)⁺

Step 8

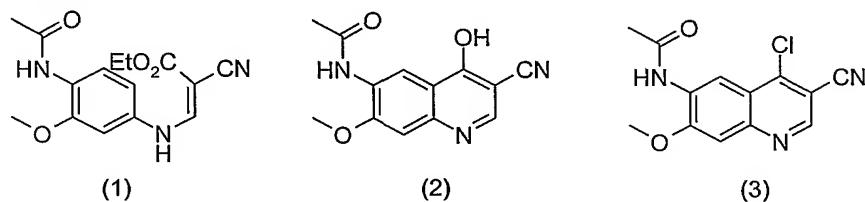
30 Intermediate (8) was reacted in 33% HBr in glacial acetic acid/thioanisole at room temperature for 2 hr to give compound 53.

Mass Spectrum m/e 482.6 (M+H)⁺

NMR Spectrum (d-6-DMSO, δ values) 1.32 (s, 6H), 2.60 (m, 3H), 2.83 (s, 3H), 6.34 (s, 1H), 6.95 – 6.99 (m, 3H), 7.07 – 7.16 (m, 4H), 7.22 – 7.31 (m, 1H), 7.37 – 7.40 (d, 2H), 8.29 – 8.32 (d, 1H), 8.86 (s, 1H).

5 Example 54

Preparation of Compound No. 54 in table 6



Step 1

Acetamide, N-(4-amino-2-methoxyphenyl) was reacted with ethyl

10 (ethoxymethylene)cyanoacetate in ethanol and refluxed for 2hr to give intermediate (1).

Mass Spectrum m/e 302.2 (M-H)⁺

Step 2

Intermediate (1) was reacted with Dowtherm A at 261°C for 210min to give intermediate (2).

Mass Spectrum m/e 256.1 (M-H)⁻

15 Step 3

Intermediate (2) was reacted with methyl cyanide in POCl_3 for 4 hr at 100°C to give intermediate (3).

Mass Spectrum m/e 275.7 (M+H)⁺

Step 4

20 Intermediate (3) was reacted with Intermediate (F), prepared as described above, in n-n-propanol solution at 100°C for 2hr to give compound 54. The product was purified by chromatography.

Mass Spectrum m/e 566.0 (M+H)⁺

NMR Spectrum (d-6-DMSO, δ values) 0.04 (m, 2H), 0.20 (m, 2H), 0.93 (s, 6H), 1.78 (s, 3H),

25 2.28 (m, 1H), 3.65 (s, 3H), 6.57 (s, 3H), 6.68 (m, 3H), 6.99 (m, 2H), 7.15 (s, 1H), 7.48 (s, 1H), 8.55 (s, 1H), 8.69 (s, 1H), 9.34 (s, 1H), 10.64 (bs, 1H)

Example 55**Preparation of Compound No. 55 in table 7**

2-(phenoxy(4-amino))4-methoxypyridine, example 56, was reacted with Intermediate A1, prepared as described above, in n-propanol solution at 100°C for 2hrs to give compound 55.

5 Mass Spectrum m/e 542.3 (M+H)⁺

NMR Spectrum (d-6-DMSO, CD₃CO₂D, δ values) 2.30 (m, 2H), 3.12 (m, 2H), 3.30 (m, 2H), 3.50 (m, 2H), 3.78 (m, 5H), 3.98 (m, 5H), 4.30 (t, 2H), 6.52 (d, 1H), 6.77 (m, 1H), 7.23 (d, 2H), 7.45 (m, 3H), 8.00 (d, 1H), 8.09 (m, 1H), 8.89 (bs, 1H)

10 **Example 56**

Preparation of Compound No. 56 in table 7**Step 1**

4-Aminophenol was reacted with 4-methoxy-2-chloropyridine in the presence of KO^tBu/18-Crown-6/DMA at 150°C for 5hrs to give 2-(4-aminophenoxy)-4-methoxypyridine. The

15 product was purified by chromatography.

Mass Spectrum m/e 217.3 (M+H)⁺

Step 2

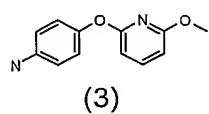
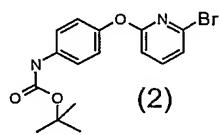
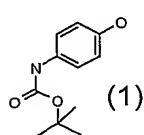
2-(4-aminophenoxy)-4-methoxypyridine was reacted with Intermedaite D, prepared as described above, in n-propanol solution at a temperature within the range 100-110°C for 330

20 min to give compound 56.

Mass Spectrum m/e 429.2 (M+H)⁺

NMR Spectrum (d-6-DMSO, CD₃CO₂D, δ values) 3.81 (s, 3H), 3.96 (d, 6H), 6.53 (d, 1H), 6.75 (m, 1H), 7.23 (d, 2H), 7.39 (s, 1H), 7.45 (d, 2H), 8.03 (m, 2H), 8.92 (bs, 1H)

25 **Example 57**

Preparation of Compound No. 57 in table 7**Step 1**

4-hydroxyaniline was reacted with Boc₂O in the presence of 1M Na₂CO₃ and THF

30 to give intermediate (1) in the above scheme.

Mass Spectrum m/e 208 (M-H)⁻.

Step 2

Intermediate (1) was reacted with 2,6-dibromopyridine in the presence of potassium-t-butoxide and DMA to give intermediate (2).

5 **Step 3**

Intermediate (2) was reacted with potassium methoxide in the presence of DMA at 100⁰C for 1 hr to give intermediate (3).

Mass Spectrum m/e 217.2 (M⁺+H).

Step 4

10 Intermediate (3) was reacted with Intermediate A1, prepared as described above, in n-proanol solution in the presence of 1M ethereal HCl at 100⁰C for 4 hr to give compound 57. The product was purified by chromatography.

Mass Spectrum m/e 542.25 (M⁺+H).

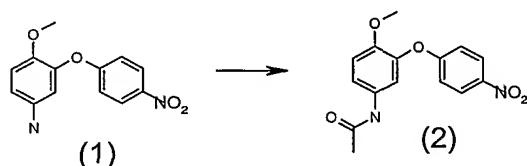
NMR Spectrum (d-6-DMSO, δ values) 2.2-2.43(m, 2H), 3.09(m, 2H), 3.28(m, 2H), 3.48(m,

15 2H), 3.7(s, 3H), 3.8(m, 2H), 3.95(m, 2H), 4.0(s, 3H), 4.3(t, 2H), 6.52(2d, 2H), 7.28(d, 2H), 7.49(d, 2H), 7.52(s, 1H), 7.73(t, 1H), 8.2(s, 1H), 8.89(s, 1H), 11.1(v.br.s, 2H).

Example 58

Preparation of Compound No. 58 in table 8

20



Step 1

5-Amino-2-methoxyphenol was reacted with 4-fluoronitrobenzene in potassium-t-butoxide and DMA at 150⁰C for 5 min to give intermediate (1).

25 Mass Spectrum m/e 261.22 (M⁺+H).

Step 2

Intermediate 1 was reacted with pyridine in the presence of acetic anhydride for 48 hr to give intermediate (2).

Mass Spectrum m/e 303.25 (M⁺+H).

Step 3

Intermediate (2) was converted to the corresponding aniline derivative by reduction with hydrogen in the presence of catalytic 5%Pd on C.

Step 4

5 The product of step 3 was reacted with Intermediate A1, prepared as described above, in n-propanol solution in the presence of 1M ethereal HCl at 100°C for 2 hr. The product was purified by chromatography (5-10% methanol/dichloromethane)

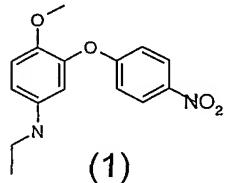
Mass Spectrum m/e 598.25 ($M^+ + H$).

NMR Spectrum (d-6-DMSO, δ values) 1.99(s, 3H), 2.31(m, 2H), 3.1(m, 2H), 3.2-3.6(m, 4H),

10 3.68(s, 3H), 3.8(t, 2H), 3.95(m, 2H), 3.98(s, 3H), 4.29(t, 2H), 6.94(d, 2H), 7.1(d, 1H), 7.34(m, 1H), 7.4(d, 2H), 7.49(d, 1H), 7.54(s, 1H), 8.19(s, 1H), 8.91(s, 1H), 9.94(s, 1H), 11.15(v.br.s, 2H).

Example 59

15 **Preparation of Compound No. 59 in table 8**

**Step 1**

Intermediate (2), example 58 was reacted with borane-THF to give intermediate (1) above.

Mass Spectrum m/e 289.18 ($M^+ + H$).

20 **Step 2**

Intermediate (1) was converted to the corresponding aniline by reduction with hydrogen in the presence of catalytic 5%Pd on C.

Step 3

The product of step 2 was reacted with Intermediate D, prepared as described above, in n-

25 propanol solution at 100°C for 2 hr to give compound 59.

Mass Spectrum m/e 471.24 ($M^+ + H$).

NMR Spectrum (d-6-DMSO, δ values) 1.15(t, 3H), 3.12(q, 2H), 3.7(s, 3H), 3.96(s, 6H),

6.88(d, 1H), 6.99(d, 3H), 7.16(d, 1H), 7.4(d, 2H), 7.43(s, 1H), 8.09(s, 1H), 8.8(s, 1H),

10.83(v.br.s, 1H).

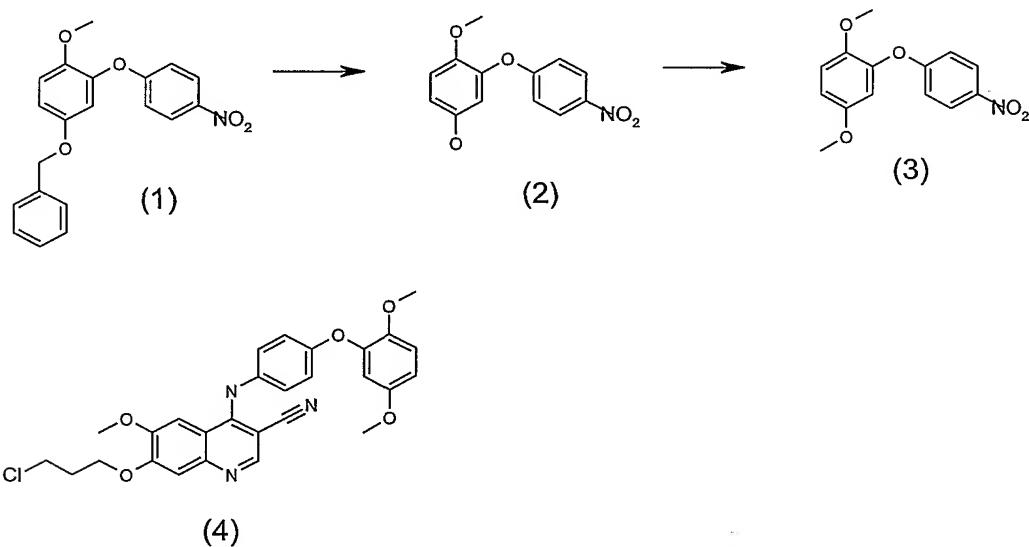
Example 60**Preparation of Compound No. 60 in table 8**

The aniline derivative of step 2 of example 59 was reacted with Intermediate A1, prepared as described above, in n-propanol solution in the presence of 1M ethereal HCl at 100°C for 2 hr 5 to give compound 60.

Mass Spectrum m/e 584.26 ($M^+ + H$).

NMR Spectrum (d-6-DMSO, δ values) 1.18(t, 3H), 2.32(m, 2H), 3.0-3.68(m, 8H), 3.73(s, 3H), 3.82(t, 2H), 3.95(m, 2H), 3.99(s, 3H), 4.29(t, 2H), 7.0(d, 2H), 7.09(m, 1H), 7.22(m, 2H), 7.4(d, 2H), 7.53(s, 1H), 8.23(s, 1H), 8.87(s, 1H), 11.16(v.br.s, 2H).

10

Example 61**Preparation of Compound No. 61 in table 8**15 **Step 1**

4-Benzyl-2-methoxyphenol was reacted with 4-fluoronitrobenzene in the presence of potassium-t-butoxide and DMA to give intermediate (1) .

Mass Spectrum m/e 299.99 ($M^+ + H$).

Step 2

20 Intermediate (1) was reacted with thioanisole in THF to give intermediate (2).

Step 3

Intermediate (2) was reacted with methyl iodide in potassium carbonate to give intermediate (3).

Step 4

Intermediate (3) was converted to the corresponding aniline derivative by reduction with hydrogen in the presence of catalytic 5%Pd on C.

Step 5

5 The aniline derivative of step 4 was reacted with Intermediate A, prepared as described above, in n-propanol solution at 100°C for 2 hr to give intermediate (4).

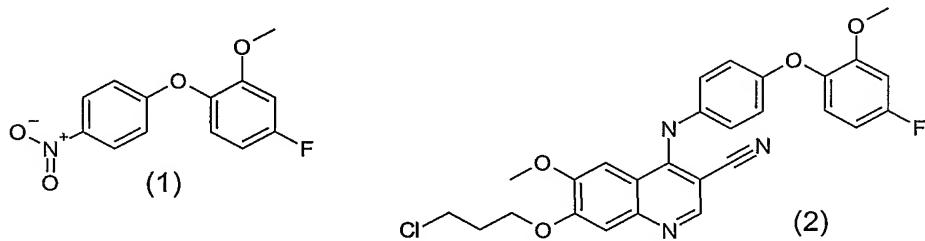
Step 6

Intermediate (4) was reacted with morpholine in sodium iodide to give compound 61. the product was purified by chromatography (10-20% Methanol/dichloromethane)

10 Mass Spectrum m/e 571.27 ($M^+ + H$).

NMR Spectrum (d-6-DMSO, δ values) 2.33(m, 2H), 3.08(m, 2H), 3.28(m, 2H), 3.48(m, 2H), 3.64(s, 3H), 3.67(s, 3H), 3.81(t, 2H), 3.95(m, 2H), 3.98(s, 3H), 4.29(t, 2H), 6.62(d, 1H), 6.73(2d, 1H), 7.0(d, 2H), 7.08(d, 1H), 7.4(d, 2H), 7.52(s, 1H), 8.08(s, 1H), 8.9(s, 1H), 11.13(v.br.s, 2H).

15

Example 62**Preparation of Compound No. 62 in table 8**

20 **Step 1**

4-Fluoro-2-methoxyphenol was reacted with KOtBu/DMA at room temperature for 20min and then with 4-fluoronitrobenzene at 150°C for 2hr to give intermediate (1).

NMR Spectrum (d-6-DMSO, δ values) 3.73 (s, 3H), 6.86 (m, 1H), 6.98 (d, 2H), 7.16 (dd, 1H), 7.25 (dd, 1H), 8.19 (d, 2H).

25 **Step 2**

Intermediate (1) was converted to the corresponding aniline derivative by reduction with hydrogen in the presence of catalytic 5%Pd on C at room temperature .

NMR Spectrum (d-6-DMSO, δ values) 3.75 (s, 3H), 4.79 (s, 2H), 6.51 (d, 2H), 6.57 - 6.70 (m, 3H), 6.79 (m, 1H), 6.99 (dd, 1H).

Step 3

The product of step 2 was then reacted with Intermediate A in n-propanol solution at 105°C
5 for 3hr to give intermediate (2)

Mass Spectrum m/e 508.24 ($M^+ + H$).

Step 4

Intermediate (2) was then reacted with piperidine in the presence of NaI at room temperature for 18hr to give compound 62. The product was purified by chromatography.

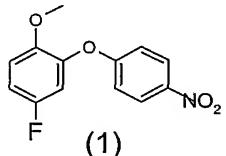
10 Mass Spectrum m/e 557.4 ($M + H$)⁺

NMR Spectrum (d-6-DMSO D4 Acetic, δ values) 1.64 – 1.89 (m, 6H), 2.30 (m, 2H), 2.91 (m, 2H), 3.20 (m, 2H), 3.48 (m, 2H), 3.72 (s, 3H), 3.97 (s, 3H), 4.28 (m, 2H), 6.74 – 6.82 (m, 1H), 6.91 – 6.98 (m, 2H), 7.05 - 7.14 (m, 2H), 7.39 (d, 2H), 7.50 (s, 1H), 8.15 (s, 1H), 8.94 (s, 1H).

15

Example 63

Preparation of Compound No. 63 in table 8.



Step 1

20 Intermediate (1), example 58 was reacted with tetrafluoroboric acid and sodium nitrite in THF in H₂O and was then heated to give intermediate (1) above.

Mass Spectrum m/e 264.17 ($M^+ + H$).

Step 2

Intermediate (1) was converted to the corresponding aniline derivative by reduction with
25 hydrogen in the presence of catalytic 5%Pd on C.

Step 3

The product of step 2 was then reacted with Intermediate D, prepared as described above, in n-propanol solution at 100°C for 2hr to give compound 63.

Mass Spectrum m/e 446.13 ($M^+ + H$).

NMR Spectrum (d-6-DMSO, δ values) 3.74(s, 3H), 3.97(s, 6H), 6.88(m, 1H), 7.0(m, 1H), 7.07(d, 2H), 7.15(m, 1H), 7.45(d, 2H), 7.47(s, 1H), 8.14(s, 1H), 8.9(s, 1H), 11.12(br.s, 1H).

Example 64

5 Preparation of Compound 64 in table 8

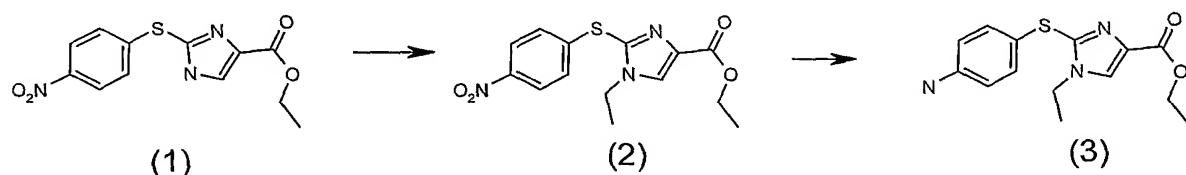
The aniline derivative of step 2, example 63 was reacted with Intermediate A1, prepared as described above in n-propanol solution in the presence of 1M ethereal HCl at 100°C for 2 hr to give compound 64. The product was purified by chromatography (5-10% Methanol/Dichloromethane).

10 Mass Spectrum m/e 559.18 ($M^+ + H$).

NMR Spectrum (d-6-DMSO, δ values) 2.33(m, 2H), 3.1(m, 2H), 3.29(m, 2H), 3.48(m, 2H), 3.73(s, 3H), 3.8(t, 2H), 3.95(m, 2H), 3.99(s, 3H), 4.29(t, 2H), 6.88(m, 1H), 7.0(m, 1H), 7.06(d, 2H), 7.16(m, 1H), 7.43(d, 2H), 7.52(s, 1H), 8.17(s, 1H), 8.89(s, 1H), 11.1(v.br.s, 2H).

15 Example 65

Preparation of Compound 65 in table 9



Step 1

20 4-Fluoro nitrobenzene and 4-ethoxy carbonylimidazole-2-thiol were reacted in the presence of Potassium t-butoxide and DMA to give intermediate (1). The product was purified by chromatography.

Mass Spectrum m/e 294 ($M^+ + H$)

Step 2

25 Intermediate (1) was reacted with methyl cyanide in the presence of NaH and EtI to give intermediate (2). The product was purified by chromatography.

Mass Spectrum m/e 322 ($M^+ + H$)

Step 3

Intermediate (2) was reacted with SnCl₂ in the presence of HCl and EtOH to give the corresponding aniline derivative.

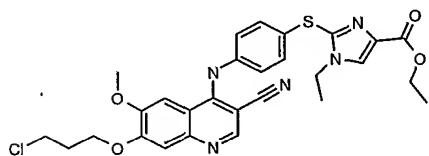
30 Mass Spectrum m/e 292 ($M^+ + H$)

Step 4

The aniline product of step 3 was reacted with Intermediate D, prepared as described above, in 1-propanol solution at 110°C for 5hr to give compound 65.

Mass Spectrum m/e 504 (M⁺+H)

5 NMR Spectrum (d-6-DMSO, δ values) 1.25 (m, 6H), 3.95 (s, 6H), 4.05 (q, 2H), 4.2 (q, 2H), 7.2 (d, 2H), 7.4 (d, 2H), 7.5 (s, 1H), 8.15 (s, 1H), 8.25 (s, 1H), 8.9 (s, 1H), 11.25 (br s, 1H)

Example 66**Preparation of compound No. 66 in table 9**

10 (1)

Step 1

The aniline derivative from step 3, example 65 was reacted with Intermediate (A) prepared as described above, in no-propanol solution at 110°C for 5hr. to give intermediate (1)

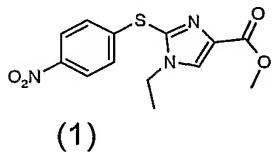
Mass Spectrum m/e 566 (M⁺+H)

15 **Step 2**

Intermediate (1) was reacted with morpholine in the presence of NaI at 50°C for 18hr to give compound 66. The product was purified by chromatography.

Mass Spectrum m/e 617 (M⁺+H)

20 NMR Spectrum (d-6-DMSO, δ values) 1.25 (t, 3H), 1.3 (t, 3H), 2.3 (m, 2H), 3.1 (m, 2H), 3.25 (m, 2H), 3.45 (m, 2H), 3.8 (t, 2H), 3.95 (m, 2H), 4.0 (s, 3H), 4.05 (m, 2H), 4.2 (q, 2H), 4.3 (q, 2H), 7.2 (d, 2H), 7.4 (d, 2H), 7.5 (s, 1H), 8.2 (s, 1H), 8.9 (s, 1H), 11.3 (br s, 2H)

Example 67**Preparation of compound No. 67 in table 9**

5

Step 1

Intermediate (1), example 68 was reacted with oxalyl chloride in the presence of DMF and MeOH to give intermediate (1) above. The product was purified by chromatography.

Mass Spectrum m/e 308 ($M^+ + H$)

10 **Step 2**

Intermediate (1) was reacted with $SnCl_2$ in the presence of HCl and EtOH to give the corresponding aniline derivative.

Mass Spectrum m/e 278 ($M^+ + H$)

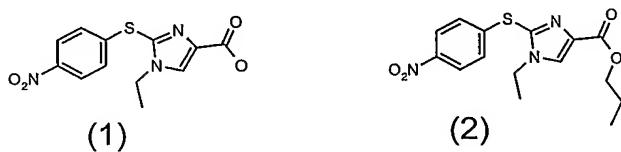
Step 3

15 The product of step 2 was reacted with Intermediate D in 1-propanol at 110°C for 5hrs to give compound 69.

Mass Spectrum m/e 490 ($M^+ + H$)

NMR Spectrum (d-6-DMSO, δ values) 1.2 (t, 3H), 3.75 (s, 3H), 3.95 (s, 6H), 4.05 (q, 2H), 7.2 (d, 2H), 7.4 (d, 2H), 7.5 (s, 1H), 8.15 (s, 1H), 8.25 (s, 1H), 8.9 (s, 1H), 11.25 (br s, 1H)

20

Example 68**Preparation of compound No. 68 in table 9****Step 1**

25 Intermediate 2, example 65 was reacted with NaOH in ethanol to give intermediate (1).

Mass Spectrum m/e 294 ($M^+ + H$)

Step 2

Intermediate (1) was reacted with oxalyl chloride in the DMF and n-propanol to give intermediate (2). The product ws purified by chromatography.

Mass Spectrum m/e 336 (M⁺+H)

5 Step 3

Intermediate (2) was reacted with SnCl₂ in the presence of HCl and EtOH to give the corresponding aniline derivative.

Mass Spectrum m/e 306 (M⁺+H)

Step 4

10 The product of step 3 was reacted with Intermediate D in 1-propanol at 110°C for 5hrs to give compound 68. The product was purified by chromatography.

Mass Spectrum m/e 518 (M⁺+H)

NMR Spectrum (d-6-DMSO, δ values) 0.95 (t, 3H), 1.25 (t, 3H), 1.7 (sextet, 2H), 3.95 (s, 6H), 4.05 (q, 2H), 4.1 (t, 2H), 7.2 (d, 2H), 7.4 (d, 2H), 7.5 (s, 1H), 8.2 (s, 1H), 8.25 (s, 1H),

15 8.95 (s, 1H), 11.35 (br s, 1H)

Assay for inhibitors of the MAP kinase pathway

To evaluate inhibitors of the MAPK pathway a coupled assay was carried out which measures phosphorylation of serine/threonine residues present in the substrate in the presence 20 or absence of inhibitor. Recombinant glutathione S-transferase fusion protein containing human p45MEK1 (GST-MEK) was activated by c-raf (Sf9 insect cell lysate from triple baculoviral infection with c-raf/ras/lck) and used for the assay. Active GST-MEK was first used to activate a recombinant glutathione S-transferase fusion protein containing p44MAP kinase (GST-MAPK) in the presence of ATP and Mg²⁺ for 60min at room temperature in the 25 presence or absence of potential inhibitors. The activated GST-MAPK was then incubated with myelin basic protein (MBP) as substrate for 10min at room temperature in the presence of ATP, Mg²⁺ and ³³P-ATP. The reaction was stopped by addition of 20% v/v phosphoric acid. Incorporation of ³³P into the myelin basic protein was determined by capture of the substrate on a filter mat, washing and counting using scintillation methods. The extent of 30 inhibition was determined by comparison with untreated controls.

The final assay solution contained 10mM Tris, pH 7.5, 0.05mM EGTA, 8.33μM [$\gamma^{33}\text{P}$]ATP, 8.33mM Mg(OAc)₂, 0.5mM sodium orthovanadate, 0.05%w/v BSA, 6.5ng GST-MEK, 1μg GST-MAPK and 16.5μg MBP in a reaction volume of 60μl.

Compounds tested of the present invention had IC₅₀ results typically less than 0.5μM.

5 For example, Compound No 3 gave an IC₅₀ of 0.0038μM.

In vitro MAP kinase assay

To determine whether compounds were inhibiting GST-MEK or GST-MAPK, a direct assay of MAPK activity was employed. GST-MAPK was activated by a constitutively active GST-MEK fusion protein containing two point mutations (S217E, S221E) and used for the 10 assay in the presence and absence of potential inhibitors. The activated GST-MAPK was incubated with substrate (MBP) for 60min at room temperature in the presence of ATP, Mg²⁺ and ³³P-ATP. The reaction was stopped by addition of 20% v/v phosphoric acid.

Incorporation of ³³P into the myelin basic protein was determined by capture of the substrate on a filter mat, washing and counting using scintillation methods.

15 The final assay solution contained 12mM Tris, pH 7.5, 0.06mM EGTA, 30μM [$\gamma^{33}\text{P}$]ATP, 10mM Mg(OAc)₂, 0.6mM sodium orthovanadate, 0.06%w/v BSA, 28ng GST-MAPK and 16.5μg MBP in a reaction volume of 60μl.

Compounds of the invention showed activity in this screen.

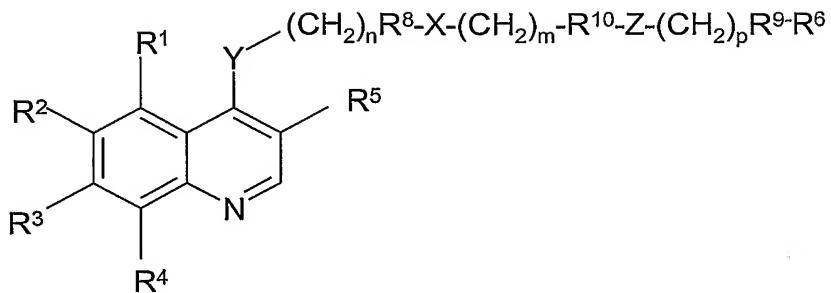
Cell proliferation assays

20 Cells were seeded into multi-well plates at 20 000 - 40 000 cells/ml in growth medium containing 5% FCS and incubated overnight at 37°C. The compounds were prepared in fresh medium at an appropriate concentration and added to the wells containing the cells. These were then incubated for a further 72 hours. Cells were then either removed from the wells by incubating with trypsin/EDTA and counted using a Coulter counter, or treated with XTT/PMS 25 in PBSA and optical densities read at 450nm. Compounds tested of the present invention had IC₅₀ results typically less than 30μM. For example, Compound No 3 gave an IC₅₀ of 1.0μM in HT29 human colon tumour cells.

CLAIMS

1. A compound of formula (I)

5



(I)

or a pharmaceutically acceptable salt, pro-drug or solvate thereof

wherein:

10 n is 0 or 1;

Y is selected from -NH-, -O-, -S-, or -NR⁷ where R⁷ is alkyl of 1-6 carbon atoms;

R⁵ is cyano, fluoro, chloro or bromo;

R⁸ is a divalent cycloalkyl of 3 to 7 carbon atoms, which may be optionally further substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a divalent pyridinyl, pyrimidinyl,

15 or phenyl ring, wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally further substituted with one or more groups selected from halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxyethyl of 2-7 carbon atoms, alkanoyloxyethyl of 2-7 carbon atoms,

alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano,

20 nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms,

alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino;

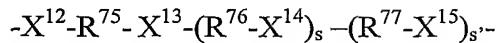
X is selected from -NH-, -O-, -S-, -CH₂- or -NR⁷ where R⁷ is alkyl of 1-6 carbon atoms;

25 m and p are independently selected from 0, 1, 2 or 3;

R¹⁰ is an optionally substituted arylene, optionally substituted C₃₋₁₀cycloalkylene ring or optionally substituted divalent heterocyclic ring or an N-oxide of any nitrogen containing ring,

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-Z- is a direct bond or a group of sub-formula (i)



(i)

where X^{12} , X^{13} each X^{14} and each X^{15} are independently selected from -O-, -C(O)-, -C(O)O-,

5 -S-, -SO-, -SO₂-, -NR⁷⁸C(O)-, -NR⁷⁸C(O)O-, -C(O)NR⁷⁹-, -C(O)ONR⁷⁹-, -SO₂NR⁸⁰-,

-NR⁸¹SO₂- or -NR⁸²- (wherein R⁷⁸, R⁷⁹, R⁸⁰, R⁸¹ and R⁸² each independently represents

hydrogen, C₁₋₃alkyl optionally substituted by hydroxy, or C₁₋₃alkoxyC₂₋₃alkyl) and each X^{13} ,

X^{14} and X^{15} may additionally be a direct bond;

s and s' are independently selected from 0, 1, 2 or 3,

10 R⁷⁵, R⁷⁶ and R⁷⁷ are independently selected from C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋₆alkynylene optionally substituted by halo and hydroxy or R⁷⁵, R⁷⁶ and R⁷⁷ can each independently be direct bonds;

R⁹ is an optionally substituted divalent heterocyclic group, C₁₋₅alkylene, or divalent C₃₋₇cycloalkyl;

15 R⁶ is hydrogen, amino or a group of sub-formula (ii)



(ii)

where X^{16} , X^{18} and each X^{17} are each independently selected from a direct bond, -O-, -C(O)-,

-S-, -SO-, -SO₂-, -NR⁸⁶C(O)-, -NR⁸⁶C(O)O-, -C(O)NR⁸⁷-, -C(O)ONR⁸⁷-, -SO₂NR⁸⁸-,

20 -NR⁸⁹SO₂- or -NR⁹⁰- (wherein R⁸⁶, R⁸⁷, R⁸⁸, R⁸⁹ and R⁹⁰ each independently represents

hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);

R⁸³ and each R⁸⁴ are independently selected from C₁₋₆alkylene, C₂₋₆alkenylene or

C₂₋₆alkynylene;

R⁸⁵ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl;

25 t is 0, 1, 2 or 3;

R¹, R², R³, R⁴ are independently selected from hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, -NR¹¹R¹²- (wherein R¹¹ and R¹², which may be the same or different, each represents hydrogen, or C₁₋₃alkyl), a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, or a group

30 R¹³-X¹-(CH₂)_x wherein x is 0 or an integer of from 1 to 3; X¹ represents a direct bond, -O-, -CH₂-, -OC(O)-, -C(O)-, -S-, -SO-, -SO₂-, -NR¹⁴C(O)-, -NR¹⁴C(O)O-, -C(O)NR¹⁵-,

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$-\text{C}(\text{O})\text{ONR}^{15}-$, $-\text{SO}_2\text{NR}^{16}-$, $-\text{NR}^{17}\text{SO}_2-$ or $-\text{NR}^{18}-$ (wherein R^{14} , R^{15} , R^{16} , R^{17} and R^{18} each independently represents hydrogen, $\text{C}_{1-3}\text{alkyl}$ or $\text{C}_{1-3}\text{alkoxyC}_{2-3}\text{alkyl}$), and R^{13} is hydrogen, optionally substituted hydrocarbyl, or optionally substituted heterocyclyl, provided that:

5 i) where the group of sub-formula (ii) is $\text{C}_{1-6}\text{alkyl}$ or R^6 is hydrogen and R^9 is a divalent heterocyclyl, Z is other than a direct bond, or the group $-\text{Z}(\text{CH}_2)_p-$ is other than C_2 alkylene, or the group of sub-formula (i) is other than $-\text{S}-$;

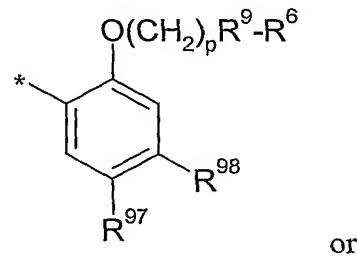
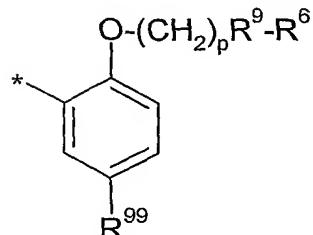
10 ii) the group R^9-R^6 cannot together be C_{1-5} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or $(\text{C}_{1-5}$ alkylene) OH unless

15 a) in the group of sub-formula (i), R^{75} or R^{76} is the group $-\text{C}(\text{R}^{\text{A}}\text{R}^{\text{B}})-$ where R^{A} and R^{B} are each independently selected from C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and halo;

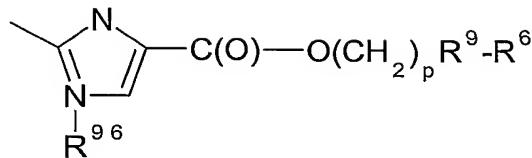
20 b) in the group of sub-formula (i), where the terminal group X^{12} , X^{13} or X^{14} linked to $-(\text{CH}_2)_p-$ or $-\text{R}^9$, is selected from $-\text{C}(\text{O})\text{NR}^{79}-$; $-\text{C}(\text{O})\text{ONR}^{79}-$; $-\text{SO}_2\text{NR}^{80}$ and $-\text{NR}^{78}\text{C}(\text{O})$; then R^{78} , R^{79} , and R^{80} are other than hydrogen but when X^{13} is $-\text{C}(\text{O})\text{NR}^{79}$ then R^{10} cannot be pyridyl;

25 c) the group of sub-formula (i) is selected from $-\text{C}(\text{O})-\text{NR}^{82}-\text{O}-$ and $-\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{NR}^{82}-\text{CH}_2-\text{C}(\text{O})\text{O}-$, where R^{82} is other than hydrogen;

d) the group $-\text{R}^{10}-\text{Z}-(\text{CH}_2)_p\text{R}^9-\text{R}^6$ is selected from



or



where R⁹⁹ is selected from -NC(O)CH₃, -NC₂H₅ or -OCH₃;

R⁹⁷ and R⁹⁸ are each independently selected from hydrogen and fluoro, provided that at least one of R⁹⁷ and R⁹⁸ is fluoro;

5

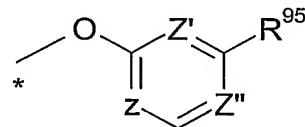
* denotes the point of attachment; and

p, R⁹ and R⁶ are as hereinbefore defined;

e) the group

10

X-(CH₂)_m-R¹⁰-Z-(CH₂)_p-R⁹-R⁶ is



where * denotes the point of attachment to R⁸;

R⁹⁵ is selected from -C(O)NR⁹⁴R⁹³ and C₁₋₆ alkoxy, where R⁹⁴ and R⁹³ each independently represent hydrogen or C₁₋₃ alkyl; and

15

Z, Z', Z'' each independently represent -CH- or nitrogen and provided that at least one of Z, Z', Z'' is nitrogen;

iii) where the group of sub-formula (i) comprises the group

20

-X¹²-R⁷⁵-X¹³-(R⁷⁶-X¹⁴)_s-(R⁷⁷-X¹⁵)_{s'}-

where X¹² is selected from -O-, -NR⁸²-, or -NR⁷⁸C(O)-;

X¹³ is selected from -C(O)NR⁷⁹, a direct bond or -NR⁸²-;

R⁷⁶, X¹⁴, R⁷⁷, X¹⁵, s and s' are as hereinbefore defined; then

25

R⁷⁵ is -C(R^AR^B)- where R^A and R^B are each independently selected from C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl and halo; unless

(i) R⁹ is piperazinyl linked through the nitrogen atoms or pyridyl;

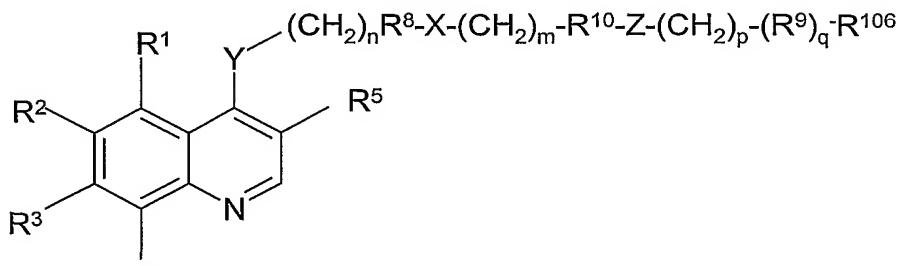
-133-

- (ii) R^{75} is 1-3 alkyl substituted by hydroxy; or
- (iii) R^{79} is other than hydrogen; or

iv) where the group of sub-formula (i) is selected from $-(CH_2)_2C(O)-$ or
5 $-O-(CH_2)_2-$ and R^9 is a divalent heterocyclic group, then R^6 is other than hydrogen.

2. A compound of formula (IA)

10



(IA)

or a pharmaceutically acceptable salt, pro-drug or solvate thereof

wherein:

15 n is 0 or 1;

Y is selected from $-NH-$, $-O-$, $-S-$, or $-NR^7-$ where R^7 is alkyl of 1-6 carbon atoms;

R^5 is cyano, fluoro, chloro or bromo;

R^8 is a divalent cycloalkyl of 3 to 7 carbon atoms, which may be optionally further substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a divalent pyridinyl, pyrimidinyl,

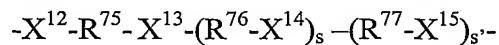
20 or phenyl ring, wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally further substituted with one or more groups selected from halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxyethyl of 2-7 carbon atoms, alkanoyloxyethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano,

25 nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino

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of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzyloxylamino; X is selected from -NH-, -O-, -S-, -CH₂- or -NR⁷- where R⁷ is alkyl of 1-6 carbon atoms; m, p and q are independently selected from 0, 1, 2 or 3

5 R¹⁰ is an optionally substituted arylene, optionally substituted C₃₋₁₀cycloalkylene ring or optionally substituted divalent heterocyclic ring or an N-oxide of any nitrogen containing ring, -Z- is a group of sub-formula (i)



(i)

10 where X¹², X¹³, each X¹⁴ and each X¹⁵ are independently selected from -O-, -C(O)-, -C(O)O-, -S-, -SO-, -SO₂-, -NR⁷⁸C(O)-, -NR⁷⁸C(O)O-, -C(O)NR⁷⁹-, -C(O)ONR⁷⁹-, -SO₂NR⁸⁰-, -NR⁸¹SO₂- or -NR⁸²- (wherein R⁷⁸, R⁷⁹, R⁸⁰, R⁸¹ and R⁸² each independently represents hydrogen, C₁₋₃alkyl optionally substituted by hydroxy, or C₁₋₃alkoxyC₂₋₃alkyl) and each X¹³, X¹⁴ and X¹⁵ may additionally be a direct bond;

15 s and s' are independently selected from 0, 1, 2 or 3;

R⁷⁵ is group -C(R^A R^B)- where R^A and R^B are each independently selected from C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl and halo;

R⁷⁶ and R⁷⁷ are independently selected from C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋₆alkynylene optionally substituted by halo and hydroxy or R⁷⁶ or R⁷⁷ can each independently be a direct

20 bond;

R⁹ is an optionally substituted divalent heterocyclic group, C₁₋₅alkylene, or divalent C₃₋₇cycloalkyl;

R¹⁰⁶ is hydrogen, hydroxy, amino or a group of sub-formula (ii)



25

(ii)

where X¹⁶, X¹⁸ and each X¹⁷ are each independently selected from a direct bond, -O-, -C(O)-, -S-, -SO-, -SO₂-, -NR⁸⁶C(O)-, -NR⁸⁶C(O)O-, -C(O)NR⁸⁷-, -C(O)ONR⁸⁷-, -SO₂NR⁸⁸-, -NR⁸⁹SO₂- or -NR⁹⁰- (wherein R⁸⁶, R⁸⁷, R⁸⁸, R⁸⁹ and R⁹⁰ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);

30 R⁸³ and each R⁸⁴ are independently selected from C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋₆alkynylene;

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R^{85} is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl;

t is 0, 1, 2 or 3;

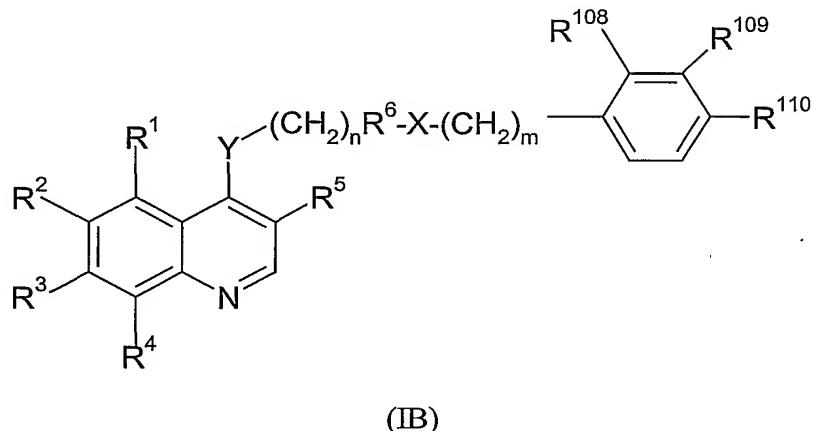
R^1, R^2, R^3, R^4 are independently selected from hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, -NR¹¹R¹²- (wherein R¹¹ and R¹², which may be the same or

5 different each represents hydrogen, or C₁₋₃alkyl), a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, or a group R¹³-X¹-(CH₂)_x wherein x is 0 or an integer of from 1 to 3, X¹ represents a direct bond, -O-, -CH₂-, -OC(O)-, -C(O)-, -S-, -SO-, -SO₂-, -NR¹⁴C(O)-, -NR¹⁴C(O)O-, -C(O)NR¹⁵-, -C(O)ONR¹⁵-, -SO₂NR¹⁶-, -NR¹⁷SO₂- or -NR¹⁸- (wherein R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ each

10 independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl)), and R¹³ is hydrogen, optionally substituted hydrocarbyl, or optionally substituted heterocyclyl.

3. A compound of formula (IB)

15



or a pharmaceutically acceptable salt, prodrug or solvate thereof

20 wherein:

n is 0 or 1;

Y is selected from -NH-, -O-, -S-, or -NR⁷- where R⁷ is alkyl of 1-6 carbon atoms;

R^5 is cyano, fluoro, chloro or bromo;

R^6 is a divalent cycloalkyl of 3 to 7 carbon atoms, which may be optionally further substituted

25 with one or more alkyl of 1 to 6 carbon atom groups; or is a divalent pyridinyl, pyrimidinyl, or

phenyl ring, wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally further substituted with one or more groups selected from halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxyethyl of 2-7 carbon atoms, alkanoyloxyethyl of 2-7 carbon atoms,

5 alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino;

10 X is selected from -NH-, -O-, -S-, -CH₂- or -NR¹⁰⁷ where R¹⁰⁷ is alkyl of 1-6 carbon atoms; m is 0, 1, 2 or 3;

R¹⁰⁸ and R¹⁰⁹ together with the carbon atoms to which they are attached form a fused 5 or 6 membered heteroaryl or heterocyclic ring ;

R¹¹⁰ is hydrogen or a group X'R¹¹⁰ where X' is NH-, -O-, -S-, -NR¹⁰⁷- where R¹⁰⁷ is alkyl

15 of 1-6 carbon atom, and R¹¹⁰ is an optionally substituted alkyl;

R¹, R², R³, R⁴ are independently selected from hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, -NR¹¹R¹²- (wherein R¹¹ and R¹², which may be the same or different each represents hydrogen, or C₁₋₃alkyl), a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, or a group

20 R¹³-X¹-(CH₂)_x wherein x is 0 or an integer of from 1 to 3, X¹ represents a direct bond, -O-, -CH₂-, -OC(O)-, -C(O)-, -S-, -SO-, -SO₂-, -NR¹⁴C(O)-, -NR¹⁴C(O)O-, -C(O)NR¹⁵-, -C(O)ONR¹⁵-, -SO₂NR¹⁶-, -NR¹⁷SO₂- or -NR¹⁸- (wherein R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), and R¹³ is hydrogen, optionally substituted hydrocarbyl, or optionally substituted heterocyclyl;

25 provided that:

i) when R¹⁰⁸ and R¹⁰⁹ together with the phenyl group form benzofuran where the heteroatom containing ring is substituted with one or more groups independently selected from C₁₋₆ alkyl, halo, hydroxyl, halo, -NR¹¹⁹R¹²⁰, C(O)NR¹¹⁹R¹²⁰ wherein R¹¹⁹ and R¹²⁰, which may be the same or different, each represent hydrogen or C₁₋₄ alkyl or C₁₋₄ cycloalkyl; and

ii) when R^{108} and R^{109} together with the phenyl group form benzodihydrofuran or benzoxazole, the heteratom containing ring is substituted with one or more groups independently selected from halo, hydroxyl, halo, $-NR^{119}R^{120}$, $-C(O)NR^{119}R^{120}$ wherein R^{119} and R^{120} , which may be the same or different each represent

5 hydrogen or C_{1-4} alkyl or C_{1-4} cycloalkyl.

4. A compound according to any one of claims 1 to 3 wherein R^1 , R^2 , R^3 and R^4 are each independently selected from hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3} alkyl, $-NR^{11}R^{12}$ (wherein R^{11} and R^{12} , which may be the same or different, each represents

10 hydrogen or C_{1-3} alkyl), a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, or a group $R^{13}-X^1-(CH_2)_x$ wherein x is 0 to 3, X^1 represents $-O-$, $-CH_2-$, $-OCO-$, carbonyl, $-S-$, $-SO-$, $-SO_2-$, $-NR^{14}CO-$, $-CONR^{15}-$, $-SO_2NR^{16}-$, $-NR^{17}SO_2-$ or $-NR^{18}-$ (wherein R^{14} , R^{15} , R^{16} , R^{17} and R^{18} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{13} is selected from one of the

15 following sixteen groups:

- 1) C_{1-5} alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, cyano and amino;
- 2) C_{1-5} alkyl X^2COR^{19} (wherein X^2 represents $-O-$ or $-NR^{20}-$ (wherein R^{20} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{19} represents $-NR^{21}R^{22}-$ or $-OR^{23}-$ (wherein R^{21} , R^{22} and R^{23} which may be the same or different each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));
- 3) C_{1-5} alkyl X^3R^{24} (wherein X^3 represents $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-OCO-$, $-CO-O-$, $-NR^{25}CO-$, $-CONR^{26}-$, $-SO_2NR^{27}-$, $-NR^{28}SO_2-$ or $-NR^{29}-$ and C_{1-5} alkyl optionally substituted by hydroxy (wherein R^{25} , R^{26} , R^{27} , R^{28} and R^{29} each independently represents hydrogen, C_{1-3} alkyl optionally substituted by hydroxy or C_{1-3} alkoxy C_{2-3} alkyl) and R^{24} represents hydrogen, amino optionally substituted by C_{1-5} alkoxycarbonyl, C_{1-5} alkyl, C_{3-6} cycloalkyl, phenyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which C_{1-5} alkyl group may bear one or two substituents selected from oxo, hydroxy, halogeno and C_{1-4} alkoxy and which cyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl and C_{1-4} alkoxy);

4) $C_{1-5}alkylX^4C_{1-5}alkylX^5R^{30}$ (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO₂-, -NR³¹CO-, -CONR³²-, -SO₂NR³³-, -NR³⁴SO₂- or -NR³⁵- (wherein R³¹, R³², R³³, R³⁴ and R³⁵ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁰ represents hydrogen, C₁₋₄alkanoyl or C₁₋₃alkyl optionally substituted by hydroxy);

5) $C_{1-5}alkylR^{36}$ (wherein R³⁶ is C₃₋₆cycloalkyl or a 4, 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which C₃₋₆cycloalkyl and heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₂₋₅alkenyl, hydroxyC₂₋₅alkenyl, C₂₋₅alkynyl, C₁₋₅alkanoyl, C₁₋₅alkoxycarbonyl, C₁₋₃alkanoylC₁₋₃alkyl, C₁₋₃alkoxyC₁₋₃alkyl, C₁₋₅alkylthio, C₁₋₅alkylsulphanyl, C₁₋₅alkylsulphonyl, aryl, hydroxyC₁₋₅alkoxy, nitro, amino, aminoC₁₋₅alkyl, guanidino, N-C₁₋₅alkylamino, N,N-di-C₁₋₅alkylamino, carboxy, cyano, cyanoC₁₋₅alkyl, -CONR^zR^{z'}- and -NR^{z''}CO- (wherein R^z, R^{z'} and R^{z''} each independently represent hydrogen, C₁₋₅alkyl or C₁₋₃alkoxyC₁₋₃alkyl);

10) $(CH_2)_qX^6R^{37}$ (wherein q is an integer from 0 to 5, X⁶ represents a direct bond, -O-, -S-, -SO₂-, -NR³⁸CO-, -CONR³⁹-, CO-O-, -SO₂NR⁴⁰-, -NR⁴¹SO₂- or -NR⁴²- (wherein R³⁸, R³⁹, R⁴⁰, R⁴¹ and R⁴² each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁷ is C₁₋₅alkoxy, a phenyl group, a benzyl group, a pyridone group or a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which phenyl, benzyl, pyridone or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, nitro, amino, N-C₁₋₅alkylamino, N,N-di-C₁₋₅alkylamino, guanidino, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄hydroxyalkoxy, C₁₋₄aminoalkyl, C₁₋₄alkylamino, carboxy, cyano, cyanoC₁₋₅alkyl, C₂₋₅alkenyl, hydroxyC₂₋₅alkenyl, C₂₋₅alkynyl, C₁₋₅alkanoyl, C₁₋₅alkoxycarbonyl, C₁₋₃alkanoylC₁₋₃alkyl, C₁₋₃alkoxyC₁₋₃alkyl, C₁₋₅alkylthio, C₁₋₅alkylsulphanyl, C₁₋₅alkylsulphonyl, aryl, -CONR⁴³R⁴⁴ and -NR⁴⁵COR⁴⁶ (wherein R⁴³, R⁴⁴, R⁴⁵ and R⁴⁶, which may be the same or different, each represents hydrogen, C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl));

20) 7) C_{2-6} alkenylR³⁶ (wherein R³⁶ is as defined hereinbefore);

25) 8) C_{2-6} alkynylR³⁶ (wherein R³⁶ is as defined hereinbefore);

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9) X^7R^{47} (wherein X^7 is $-SO_2-$, $-O-$ or $-CONR^{48}R^{49}-$ (wherein R^{48} and R^{49} , which may be the same or different, each represents hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{47} represents $C_{1-5}alkyl$ which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino) with the provisos that when X^7 is $-SO_2-$, X^1 is $-O-$, when X^7 is $-O-$, X^1 is carbonyl, or when X^7 is $-CONR^{48}R^{49}-$, X^1 is $-O-$ or NR^{18} (wherein R^{48} , R^{49} and R^{18} are as defined hereinbefore);

5) 10) $C_{2-6}alkenylR^{37}$ (wherein R^{37} is as defined hereinbefore);

11) $C_{2-6}alkynylR^{37}$ (wherein R^{37} is as defined hereinbefore);

12) $C_{2-6}alkenylX^8R^{37}$ (wherein X^8 represents $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{50}CO-$, $-CONR^{51}-$, $-SO_2NR^{52}-$, $-NR^{53}SO_2-$ or $-NR^{54}-$ (wherein R^{50} , R^{51} , R^{52} , R^{53} and R^{54} each independently represents hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{37} is as defined hereinbefore);

10) 13) $C_{2-6}alkynylX^9R^{37}$ (wherein X^9 represents $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{55}CO-$, $-CONR^{56}-$, $-SO_2NR^{57}-$, $-NR^{58}SO_2-$ or $-NR^{59}-$ (wherein R^{55} , R^{56} , R^{57} , R^{58} and R^{59} each independently represents hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{37} is as defined hereinbefore);

15) 14) $C_{1-3}alkylX^{10}C_{1-3}alkylR^{37}$ (wherein X^{10} represents $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{60}CO-$, $-CONR^{61}-$, $-SO_2NR^{62}-$, $-NR^{63}SO_2-$ or $-NR^{64}-$ (wherein R^{60} , R^{61} , R^{62} , R^{63} and R^{64} each independently represents hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{37} is as defined hereinbefore);

15) 15) R^{36} (wherein R^{36} is as defined hereinbefore); and

20) 16) $C_{1-3}alkylX^{10}C_{1-3}alkylR^{36}$ (wherein X^{10} and R^{36} are as defined hereinbefore).

5. A compound according to claim 1 wherein R^{10} is an optionally substituted arylene or an optionally substituted divalent heterocyclic ring;

Z is a direct bond or a group of sub-formula (i)

25 $-X^{12}-R^{75}-X^{13}-(R^{76}-X^{14})_s-(R^{77}-X^{15})_s,-$
 (i)

where X^{12} , X^{13} , X^{14} , X^{15} , R^{76} , R^{77} , s and s' are as hereinbefore defined and R^{75} is the group –
 $C(R^A R^B)$ - where R^A and R^B are each independently selected from C_{1-3} alkyl, C_{2-3} alkenyl,
 C_{2-3} alkynyl and halo; p is 0 or 1; and R^6 is hydrogen.

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6. A compound according to claim 1 wherein in the group of sub-formula (i), R⁷⁵ is the group -C(R^A R^B) where R^A and R^B are each independently selected from C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl and halo.

5 7. A compound according to claim 6 wherein R^A and R^B are each independently selected from C₁₋₃ alkyl and halo.

8. A compound according to claim 6 wherein R^A and R^B are both either C₁ alkyl or fluoro.

10

9. A compound according to claims 1 or 2 wherein in the group of sub-formula (i), X¹³ is -C(O)NR⁷⁹- where R⁷⁹ is hydrogen or -CH₂-.

10. A compound according to claims 1 or 2 wherein R⁷⁶ is a direct bond or is -CH₂-.

15

11. A compound according to claims 1 or 2 wherein R¹⁰ is a divalent phenyl.

12. A compound according to claims 1 or 2 wherein R⁶ is hydrogen.

20 13. A compound according to claims 1 or 2 wherein R¹⁰ is substituted with at least one fluoro group.

14. A compound according to claims 1 or 2 or 3 wherein R⁵ is cyano.

25

15. A compound according to claim 2 wherein the group of sub-formula (i) is selected from -O-C(CH₃)₂-CONR⁷⁹- ;

-O-C(F)₂- ;

-O-C(CH₃)₂-CONR⁷⁹-CH₂-CONR⁷⁹- ;

30 -O-C(CH₃)₂-CONR⁷⁹-CH₂-CONR⁷⁹-(CH₂)₂-NR⁸²- ;

-O-C(F)₂-CONR⁷⁹- ;

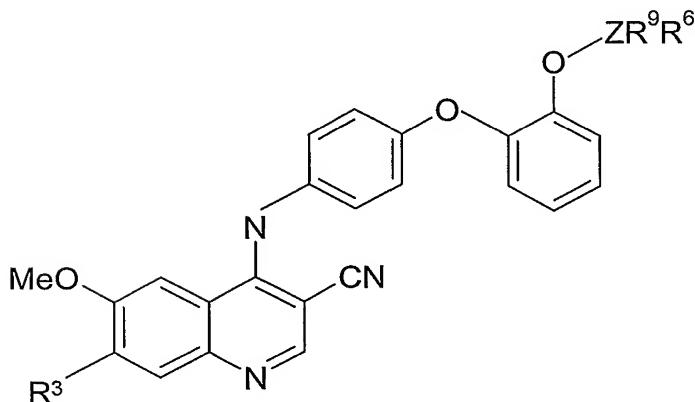
-141-

-O-C(F)₂-CONR⁷⁹-CH₂-CONR⁷⁹- ;
 -O-C(CH₃)₂-CONR⁷⁹-CH₂-NR⁸²- ;
 -O-C(CH₃)₂-CONR⁷⁹-(CH₂)₂-SO₂- ;
 -O-C(CH₃)₂-CONR⁷⁹-(CH₂)₂-S- ; and
 -O- C(CH₃)₂-CONR⁷⁹-(CH₂)₂-O-

5

wherein R⁷⁹ and R⁸² are as defined in relation to claim 2.

16. A compound of formula (IE)



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(IE)

or a pharmaceutically acceptable salt, prodrug or solvate thereof

and wherein R³, Z, R⁹ and R⁶ are selected from the following groups:

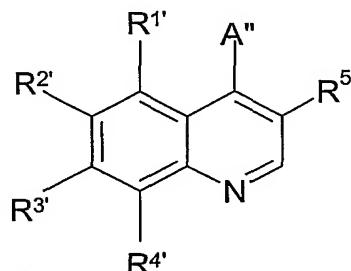
- i) R³ is -OCH₃, Z is the group -O-C(CH₃)₂-CONH-CH₂-CONH-, the group R⁹-R⁶ is -C₂H₅;
- 15 ii) R³ is -OCH₃, Z is the group -O-C(CH₃)₂-CONH-CH₂-CONH-, the group R⁹-R⁶ is cyclobutyl;
- iii) R³ is H, Z is the group -O-C(CH₃)₂-CONH, the group R⁹-R⁶ is CH₃;
- iv) R³ is H, Z is the group -O-C(CH₃)₂-CONH-CH₂-CONH-, the group R⁹-R⁶ is CH₃;
- v) R³ is -OCH₃, Z is the group -O-C(CH₃)₂-CONH-CH₂-CON(CH₃)-, the group R⁹-R⁶ is -CH₃;
- 20 vi) R³ is -OCH₃, Z is the group -O-C(CH₃)₂-CONH-CH₂-CONH-, the group R⁹-R⁶ is cyclopropyl;
- vii) R³ is -OCH₃, Z is the group -O-C(CH₃)₂-CONH-CH₂-CONH-CH₂, the group R⁹-R⁶ is cyclopropyl;

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- viii) R^3 is $-OCH_3$, Z is the group $-O-C(CH_3)_2-CONH-CH_2-CONH-CH_2$, the group R^9-R^6 is CH_3 ;
- ix) R^3 is $-NHCH_3$, Z is the group $-O-C(CH_3)_2-CONH-$; the group R^9-R^6 is CH_3 ;
- x) R^3 is $-OCH_3$, Z is the group $-O-C(CH_3)_2-(CH_2)_2-$, the group R^9-R^6 is pyridine;
- 5 xi) R^3 is $-NHCH_3$, Z is the group $-O-C(CH_3)_2-CONH-$, the group R^9-R^6 is cyclopropyl;
- xii) R^3 is $-OCH_3$, Z is the group $-O-C(CH_3)_2-CONH-CH_2-CONH-(CH_2)_2-N(CH_3)-$, the group R^9-R^6 is $-CH_3$; and
- xiii) R^3 is 3-(1-morpholino)propoxy, Z is the group $-O-C(CH_3)-CONH-$, the group R^9-R^6 is $-(CH_2)_2OH$.

17. A process for the preparation of a compound of formula (I), (IA) or (IB) which comprises the reaction of

15 a) a compound of formula (II)

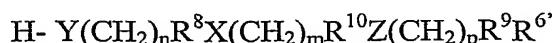


(II)

20

wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ represent R^1 , R^2 , R^3 and R^4 as defined in claim 1, R^5 is as defined in claim 1 and A'' is a leaving group, with a compound formula (III)

25

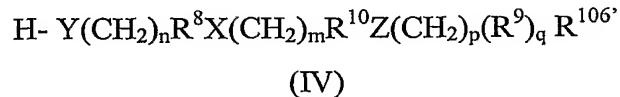


(III)

-143-

wherein Y, n, R⁸, X, R¹⁰, m, Z, p and R⁹ are as defined in claim 1 and R^{6'} is a group as defined in claim 1 or a precursor thereof or with a compound formula (IV)

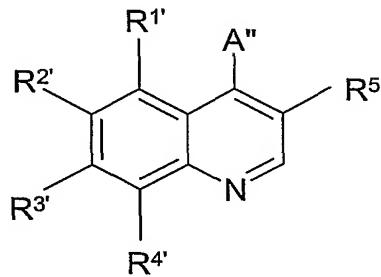
5



wherein Y, n, R⁸, X, R¹⁰, m, Z, p, q and R⁹ are as defined in claim 1 and R^{106'} is a group as defined in claim 2 or a precursor thereof and thereafter, if necessary, converting precursor groups R^{1'}, R^{2'}, R^{3'}, R^{4'}, R^{6'} and R^{106'} to groups of formula R¹, R², R³, R⁴, R⁶ and R¹⁰⁶ respectively or converting a group R¹, R², R³, R⁴, R⁶, R¹⁰⁶ to a different such group; or

15

b) a compound of formula (V)



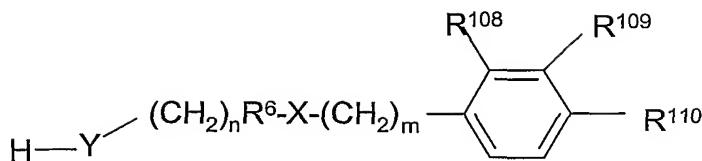
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(V)

where R^{1'}, R^{2'}, R^{3'}, R^{4'} represent R¹, R², R³ and R⁴ respectively as defined in claim 3 or a precursor thereof, R⁵ is as defined in claim 3 and A'' is a leaving group

with a compound of formula (VI)

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(VI)

5

where Y, n, R⁶, X, m, R¹⁰⁸, R¹⁰⁹, and R¹¹⁰ are as defined in claim 3 and thereafter, if necessary, converting precursor groups R^{1'}, R^{2'}, R^{3'} and R^{4'} to groups of R¹, R², R³ and R⁴; and when a pharmaceutically acceptable salt of compound of formula (I), (IA) or (IB) is required it may be obtained using a conventional procedure.

10

18. A pharmaceutical composition which comprises a compound of formula (I), (IA) or (IB), (IE) or a pharmaceutically acceptable salt, pro-drug or solvate as defined in claims 1, 2 3 or 16 in association with a pharmaceutically-acceptable diluent or carrier.

15 19. A compound of the formula (I), (IA), (IB) or (IE) or a pharmaceutically acceptable salt, pro-drug or solvate thereof as defined in claims 1,2, 3 or 16 for use in the method of treatment of the human or animal body by therapy.

20. The use of a compound of the formula (I), (IA), (IB) or (IE) or a pharmaceutically acceptable salt, pro-drug or solvate thereof as defined in claims 1, 2, 3 or 16 in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

INTERNATIONAL SEARCH REPORT

In	Application No
PCT/GB 01/04733	

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07D215/54	C07D413/12	C07D401/12	C07D405/12	A61K31/4709
A61P35/00					

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
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EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT
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Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 18761 A (AMERICAN CYANAMID CO) 6 April 2000 (2000-04-06) examples ----	3,16-20
Y	WO 98 43960 A (AMERICAN CYANAMID CO) 8 October 1998 (1998-10-08) cited in the application page 101; claim 1 ----	3,16-20
Y	WO 96 09294 A (WELLCOME FOUND ;HUDSON ALAN THOMAS (GB); VILE SADIE (GB); BARRACLO) 28 March 1996 (1996-03-28) the whole document ----	3,16-20
P, Y	WO 00 68201 A (POYSER JEFFREY PHILIP ;TURNER PAUL (GB); BOYLE FRANCIS THOMAS (GB)) 16 November 2000 (2000-11-16) the whole document ----	3,16-20
	-/-	

<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.
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<input checked="" type="checkbox"/> Patent family members are listed in annex.
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* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

28 January 2002

Date of mailing of the international search report
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04/02/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer

Lauro, P

INTERNATIONAL SEARCH REPORT

Inl Application No
P01/00 01/04733

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 00 68199 A (GIBSON KEITH HOPKINSON ; ASTRAZENECA AB (SE)) 16 November 2000 (2000-11-16) the whole document -----	3, 16-20

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-2,4-15

Present claims 1-2,4-15 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely compounds have been searched which are recited in the examples and closely related homologous compounds, i.e. those mentioned in the description at pages 12, 40-41 in Formulae (IB), (IE) (wherein the group Z is assumed to be directly attached to the phenyl ring and not as indicated in the formula to an oxygen atom) and (IF). Pro-drug forms have also not been searched, since their structure is undefined.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/GB 01/04733

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0018761	A	06-04-2000	AU BR CN CZ EP NO WO	6159399 A 9914167 A 1320121 T 20011038 A3 1117659 A1 20011575 A 0018761 A1	17-04-2000 19-06-2001 31-10-2001 12-09-2001 25-07-2001 28-05-2001 06-04-2000
WO 9843960	A	08-10-1998	AU CN EP HU JP NO PL SK TR WO ZA	6877798 A 1259125 T 0973746 A1 0002112 A2 2001519788 T 994798 A 335999 A1 135799 A3 9902946 T2 9843960 A1 9802771 A	22-10-1998 05-07-2000 26-01-2000 28-09-2000 23-10-2001 24-11-1999 05-06-2000 16-05-2000 21-03-2000 08-10-1998 01-10-1999
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WO 0068201	A	16-11-2000	AU WO	4589100 A 0068201 A1	21-11-2000 16-11-2000
WO 0068199	A	16-11-2000	AU WO	4589200 A 0068199 A1	21-11-2000 16-11-2000